HEALTH EFFECTS OF COAL TAR PRODUCTS AND BITUMENS

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EXECUTIVE SUMMARY

This report is a comprehensive review of the available scientific evidence relating to the health effects of coal tar, coal tar pitch, creosote, petroleum pitch, bitumen and asphalt, six substances which contain polynuclear aromatic hydrocarbons, (PAH's). Segments of the literature are critically appraised in terms of quality of evidence and interpretation.

Chapter I contains the introduction and definitions. The six above-mentioned substances are briefly described and placed in historical perspective.

Chapter II focuses on the pharmacokinetics of polynuclear aromatic hydrocarbons. The major routes of polycyclic aromatic hydrocarbon absorption are through inhalation and cutaneous exposure. Once absorbed they are distributed throughout the body via the circulatory system. Metabolic studies using benzo[a]pyrene as a model for PAH metabolism demonstrate that PAH's are metabolized and biotransformed through the cytochrome P-450 system. The removal of the PAHs from the body is mainly through the liver, biliary tract and the elimination of feces.

Chapter III summarizes a number of experimental studies on the acute and chronic effects of coal tar products, asphalt and bitumens both in humans and animals. Most of these studies report apparent acute effects of these complex mixtures primarily on the skin and eyes. The literature is flooded with old and recent reports of photo-toxic skin reactions and several ocular

manifestations ranging from marked photophobia to severe keratoconjunctivitis. In some of the studies, respiratory distress such as nasal congestion, hoarseness, throat irritation, coughing, nose and throat inflammation and congestion due to exposure to coal tar pitch dusts are also described. All these effects require immediate attention in considering the health effects of workplace exposures and require preventive measures.

Chapter IV reviews a substantial number of studies of animal carcinogenesis associated with exposure to coal tar and petroleum products and coke oven emissions. Coal tar, coal tar pitch and coke oven emissions result in the formation of skin tumours and/or lung tumours in animals. There are conflicting reports in the animal carcinogenesis experimental studies of creosote and asphalt. Some of the studies in this category contained substantial limitations including a lack of specification of test groups, (e.g., age, sex, and strain), relatively small test groups, the absence of a concurrent control group, the omission of the dose administered, and the absence of survival data. Section 4.2 considers mutagenicity studies of coal tar, coal tar pitch, creosote, coke oven emissions and asphalt. Most of these studies report that the compounds were mutagenic.

Chapter V is an exhaustive review of the literature pertaining to the adverse effects of benzo[a]pyrene exposure on reproduction in animals. Metabolic considerations, mutagenicity, effects on estrous cycle, uterus and ovary, testicular effects, effects on fertility, transfer across placental and mammary

glands, embryotoxicity, fetotoxicity and teratogenicity, and transplacental carcinogenesis are discussed in separate sections of the chapter. The available evidence in the literature regarding the adverse reproductive effects of coal tar and related exposures, though limited, suggests potential risks for most types of reproductive outcomes. There have been no studies involving human exposure.

Chapter VI is a compilation of case report studies of human carcinogenesis associated with exposure to coal tar and petroleum products. Some of the early case reports summarized in 6.1, which date back to the early 19th century, report finding skin and scrotal cancers. Section 6.2 summarizes epidemiologic studies of cancer in human populations and their relation to environmental and occupational exposures to coal tar products, petroleum products, and other factors. One of the most common difficulties encountered in conducting and interpreting epidemiologic studies is the control of confounding factors, especially cigarette smoking, thus limiting the usefulness of such studies in assessing the carcinogenic dose-response relationship of the substances under consideration outlined in Section 6.3. Nevertheless, there is sufficient evidence concerning the human carcinogenic potential of coal tar products in the literature to warrant stringent control of workplace exposures.

The final chapter contains an analysis of the risks associated with exposures to coal tar and petroleum products, and recommendations for an exposure standard. The advantages

and disadvantages of different risk estimate approaches are discussed in Section 7.2. The major problems associated with the extrapolation of toxicological data from animals to man are also discussed. Risk assessment and the establishment of accurate Threshold Limit Values (TLVs) for complex mixtures of PAH's are extremely difficult.

Approaches to biological monitoring are reviewed in Section 7.4. Section 7.5 examines considerations of exposure quantification. The relative contributions of cigarette smoke and air pollution to lung cancer mortality in the community are reviewed. With respect to measurement, a dual sampling and analysis technique involving the conventional cyclohexane soluble method and high performance liquid chromatography (HPLC) with a UV detector and fluorescence method is recommended in Section 7.6. The main advantage of this approach is that it provides both a quantitative and qualitative analysis for PAH's.

In the concluding section of chapter 7, it is proposed that an acceptable interim standard to limit occupational exposure to coal tar pitch volatiles from all forms of coal tar products including creosote would be 0.05 mg/m^3 cyclohexane soluble extract timeweighted average over an 8 hour working day. With respect to asphalt fumes, a standard of 0.5 mg/m^3 time-weighted average over an 8 hour period is recommended. A work practice standard should be made to limit dermal exposure to coal tar products such as creosote to zero exposure if no substitution compound is available at this time. Although human evidence is

lacking with regard to reproductive hazards, the regulation must address this potential risk.

The measurement of exposure profiles of complex mixtures of PAH's in industry is needed and should be given high priority. Refinement of the exposure standard can be made based on this information. Further epidemiological research is required to define the health risks from these substances with greater certainty.

CHAPTER ONE

INTRODUCTION AND DEFINITIONS

1.1 Scope and Definitions

The health effects of a number of substances, all of which are complex mixtures containing polynuclear aromatic compounds (PACs) - coal tars, coal tar pitch, creosotes, petroleum pitch, bitumens, and asphalt are reviewed in this document with the purpose of providing background information to the Special Studies and Services Branch of the Ontario Ministry of Labour. The overall objective of the project is to summarize the evidence concerning the health effects of these substances. This report provides background information to allow the reader to interpret some of the research without having to refer to original reports. Descriptions of the research are made throughout the text and some critical assessment of the quality of the evidence and interpretations thereof are included and summarized at the end of each chapter.

1.2 Descriptions of the Substances Reviewed

1.2.1 Coal Tars and Derived Products

Coal tars are byproducts of the destructive distillation of coal. This process is called carbonization or coking. The composition and properties of coal tar depend on the temperature of carbonization and the nature of the coal used as the raw material. Coal tars are usually present in industry as a viscous liquid or semisolid and are black in color. They have a characteristic naphthalene-like odor.

Coal tars are complex combinations of various hydrocarbons, phenols, sulphur and nitrogen compounds and heterocyclic oxygen compounds. There may be as many as 10,000 different compounds in coal tar and they vary greatly depending on the temperature. McNeil (1983) has summarized the processes involved in coal tar production and outlined the many compounds that have been identified.

The important common distillation fractions and residues from coal tars made by the high-temperature and low-temperature processes, as well as information on their main components, are given in Table I - 1.

Table I - 2 shows some of the main components of selected coal tars and also compares the main components made by high-temperature and low-temperature processes. High-temperature coal tars are the condensation products obtained by the cooling

Table I - 1. Properties of primary distillation fractions and residues from coal tars*

Chemical Abstracts Name	Chemical Abstracts Services Registry Number	Distillation range (deg C)	Main Components
A. Products derived from high-temperature (>700 deg C) coal-tars			
Light oil/ overheads	65996-78-3	<180	Mainly toluene, xylenes, benzene and indene-naphtha
Carbolic oil		180-205	Mainly higher alkyl-benzenes, phenol and alkylphenols, indene, xylene and naphthalene
Naphthalene oil		200-230	Mainly naphthalene and methylnaphtha-lene plus smaller proportions of alkylbenzenes, thio-naphthalene and alkylphenols; usually alkaline washed to recover the acids; pure naphthalene may be recovered by crystallization and centrifugation
Creosote oil/ wash oil	8001-58-9	230-290	Mainly alkylnaphtha lenes, diphenylace-naphthene, fluorene, plus small amounts of higher phenols
Light anthracene oil		260-310	Mainly anthracene, phenanthrene and carbazole, with small amounts of fluorene and pyrene; an anthracene-rich fraction may be recovered by

cont'd

Table I - 1
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			crystallization and centrifugation
Heavy anthracene oil/base oil		>310	Mainly polynuclear aromatic compounds of higher molecular weight
Medium-soft pitch	65996-93-2	Residue	40-50% of polynuclear aromatic compounds with 4-7 rings
B. Products derived from low-temperature (<700 deg C) coal-tars			
Light oil		90-160	Primarily C6-C10 hydrocarbons
Middle oil		160-240	Primarily phenols, hydrocarbons and aromatic nitrogen bases
Heavy/wax oil		240-360/ 235-450	Both contain hydrocarbons, heavy oil and phenols
Pitch		Residue	Principally polynuclear aromatic compounds and phenols

* Based on McNeil (1983)

Table I - 2. Some constituents of coal tars*

	Average weight % of dry tar					
	High-temperature processes				Low-temperature processes	
	Coke oven tars			CVR ** tars	Conventional low-temperature tars	Lurgi tars
	UK	FRG	USA	UK	UK	UK
Benzene	0.25	0.4	0.12	0.22	0.01	0.02
Toluene	0.22	0.3	0.25	0.22	0.12	0.05
ortho-Xylene	0.04	-	0.04	0.06	0.05	0.05
meta-Xylene	0.11	0.2	0.07	0.13	0.10	0.07
para-Xylene	0.04	-	0.03	0.05	0.05	0.03
Ethylbenzene	0.02	-	0.02	0.03	0.02	0.04
Styrene	0.04	-	0.02	0.04	0.01	0.01
Phenol	0.57	0.5	0.61	0.99	1.44	0.07
ortho-Cresol	0.32	0.2	0.25	1.33	1.48	1.14
meta-Cresol	0.45	0.4	0.45	1.01	0.98	1.83
para-Cresol	0.27	0.2	0.27	0.86	0.87	1.51
Xylenols	0.48	-	0.36	3.08	6.36	5.55
High-boiling tar acids	0.91	-	0.83	8.09	12.89	11.95
Naphtha	1.18	-	0.97	3.21	3.63	3.02
Naphthalene	8.94	10.0	8.80	3.18	0.65	2.01
a-methyl-naphthalene	0.72	0.5	0.65	0.54	0.23	0.63
b-methyl-naphthalene	1.32	1.5	1.23	0.68	0.19	1.05
Acenaphthene	0.96	0.3	1.05	0.66	0.19	0.57
Fluorene	0.88	2.0	0.64	0.51	0.13	0.62
Diphenylene oxide	1.50	1.4	-	0.68	0.19	0.57
Anthracene	1.00	1.8	0.75	0.26	0.06	0.32
Phenanthrene	6.30	5.7	2.66	1.75	1.60	0.28
Carbazole	1.33	1.5	0.60	0.89	1.29	0.22
Tar bases***	1.77	0.73	2.08	2.09	2.09	2.50
Medium-soft pitch	59.8	54.4	63.5	43.7	26.0	33.1

* From McNeil (1983)

** CVR, continuous vertical-retort process

*** Tar bases include quinoline, isoquinoline, methylquinolines, pyridine, x- and b-picolines, ethylpyridine and lutidines; only a minority of the basic constituents in CVR and low-temperature tars have been identified.

of the gas evolved in the high-temperature (over 700°C) carbonization of coal. Low-temperature coal tars are the condensation products obtained by cooling of the gas evolved in low temperature (below 700° C) carbonization of coal.

Most importantly, more than 200 different types of polycyclic aromatic hydrocarbons have been identified, especially in high temperature coal tars and their concentrations, are crucial in considering the health effects of exposure to coal tars.

PAH concentrations found in high-temperature coal tars are as shown in Table I - 3. Data from several studies on coal-tars are summarized in Table I - 4, and PAHs found in high-temperature coal-tar pitches in various studies are summarized in Table I - 5.

Table I - 3. Concentrations (%) of polynuclear aromatic hydrocarbons (PAH) found in high-temperature coal tars*

PAH	Concentration %	PAH	Concentration %
Naphthalene	10	Benzo[a]pyrene	0.50
Anthracene	1.5	Benzo[a]fluoranthene	0.30
Phenanthrene	5.0	Benzo[b]fluoranthene	0.30
Pyrene	2.1	Benzo[j]fluoranthene	0.30
Fluoranthene	3.3	Benzo[k]fluoranthene	0.40
Tetracene (naphthacene)	0.25	Dibenz[a,j]anthracene	0.10
Benz[a]anthracene	0.65	Dibenz[a,h]anthracene	0.10
Chrysene	1.1	Picene	0.15
Triphenylene	0.13	Benzo[ghi]perylene	0.55
Perylene	0.25	Anthanthrene	0.18
Benzo[a]pyrene	0.55	Indeno[1,2,3-cd]pyrene	0.50

* From Kleffner et al. (1981)

Table I - 4. Polynuclear aromatic hydrocarbons (PAHs) found in high temperature coal tars*

PAH	Type of coal tar	PAH concentration (ug/kg)	Reference
Anthracene	Pharmaceutical	2880-4350	Lijinsky et al. (1963)
	Crude	11,000	Mariich & Lenkevich (1973)
Benz[a] anthracene	Pharmaceutical	6240-6980	Lijinsky et al. (1963)
	Samples from Detroit	210-602	Colucci & Begeman (1965)
Benzo[b] chrysene	Pharmaceutical	800-930	Lijinsky et al. (1963)
Benzo[b] fluoranthene	Crude	Detected	Kruber & Oberkobusch
	Samples from Detroit	209-492	Colucci & Begeman (1965)
Benzo[j] fluoranthene	Pharmaceutical	450-630	Lijinsky et al. (1963)
	Samples from Detroit	62-205	Colucci & Begeman (1965)
Benzo[k] fluoranthene	Pharmaceutical	1070-1080	Lijinsky et al. (1963)
	Samples from Detroit	86-608	Colucci & Begeman (1965)
Benzo[ghi] perylene	Pharmaceutical	1230-1890	Lijinsky et al. (1963)
	Samples from Detroit	317-664	Colucci & Begeman (1965)
Benzo[a]pyrene	Pharmaceutical	1760-2080	Lijinsky et al. (1963)
	Experimental	149	Tomkins et al. (1980)
	Crude	500	Zorn (1978)
	Samples from Detroit	93-354	Colucci & Begeman (1965)
Benzo[e]pyrene	Pharmaceutical	1850-1880	Lijinsky et al. (1963)
Chrysene	Pharmaceutical	2130-2860	Lijinsky et al. (1963)
	Crude	5600	Mariich & Lenkevich (1973)
	Samples from Detroit	99-728	Colucci & Begeman (1965)
Dibenz[a,c] anthracene	Crude	Detected	Lang et al. (1959)

cont'd

Table I - 4
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Dibenz[a,h] anthracene	Pharmaceutical	230-300	Lijinsky et al. (1963)
	Crude	Detected	Lang et al. (1959)
Dibenz[a,j] anthracene	Crude	Detected	Lang et al. (1959)
Dibenz[a,i] pyrene	Crude	Detected	Schoental (1957)
Fluoranthene	Pharmaceutical	17700-17 800	Lijinsky et al. (1963)
	Crude	21-500	Mariich & Lenkevich (1973)
	Samples from Detroit	94-820	Colucci & Begeman (1965)
Fluorene	Crude	13 700	Mariich & Lenkevich (1973)
Indeno[1,2,3-cd]pyrene	Crude	Detected	Lang et al. (1959)
	Samples from Detroit	135-457	Colucci & Begeman (1965)
Perylene	Pharmaceutical	700-760	Lijinsky et al. (1963)
Phenanthrene	Pharmaceutical	13 600-17 500	Lijinsky et al. (1963)
	Crude	43 000	Mariich & Lenkevich (1973)
Pyrene	Pharmaceutical	7950-10 500	Lijinsky et al. (1963)
	Crude	12 300	Mariich & Lenkevich (1973)
	Samples from Detroit	144-1045	Colucci & Begeman (1965)

* From IARC (1985)

Table I - 5. Polynuclear aromatic hydrocarbons (PAHs) found in high-temperature coal tar pitches*

PAH	Use of coal tar pitch	PAH concentration (mg/kg)	Reference
Anthracene	Not given	1.5	Gorman & Liss (1985)
Anthracene and/or phenanthrene	Roofing	34 000	Hervin & Emmett (1976)
Benz[a]anthracene	Not given	8.4	Gorman & Liss (1985)
	Roofing	8900-12 500	Wallcave et al. (1971)
	Roofing	169 000-324 000	Malaiyandi et al. (1982)
Benz[a]anthracene	Roofing	16 000	Hervin & Emmett (1976)
Benzo[b] fluoranthene	Not given	22.4	Gorman & Liss (1985)
Benzo[ghi] fluoranthene	Electrodes	400-3400	Arrendale & Rogers (1981)
Benzo[k]fluoranthene	Not given	11.2	Gorman & Liss (1985)
	Roofing	1670-4500	Malaiyandi et al. (1982)
	Roofing	12 000	Hervin & Emmett (1976)
Benzo[ghi] perylene	Roofing	754-3980	Malaiyandi et al. (1982)
Benzo[a]pyrene	Not given	16	Gorman & Liss (1985)
	Electrodes	4500-13 200	Arrendale & Rogers (1981)
	Roofing	8400-12 500	Wallcave et al. (1971)
	Roofing	4290-11 000	Malaiyandi et al. (1982)
Benzo[a]pyrene and benzo[e]pyrene	Roofing	10 000	Hervin & Emmett (1976)
Benzo[e]pyrene	Not given	14.3	Gorman & Liss (1985)
	Roofing	5400-7000	Wallcave et al. (1971)
Chrysene	Not given	19.6	Gorman & Liss (1985)
	Electrodes	2600-17 000	Arrendale & Rogers (1981)
	Roofing	42 500-88 000	Malaiyandi et al. (1982)
	Roofing	7400-10 000	Wallcave et al. (1971)
Dibenz[a,c] anthracene	Not given	Detected	Lang et al. (1959)

cont'd

Table I - 5
cont'd...page 2

Dibenz[a,h] anthracene	Not given	Detected	Lang et al. (1959)
	Roofing	317-1680	Malaiyandi et al. (1982)
Dibenz[a,j] anthracene	Not given	Detected	Lang et al. (1959)
7,12-Dimethylbenz-[a]anthracene	Roofing	1070-2950	Malaiyandi et al. (1982)
Fluoranthene	Electrodes	5200-38 800	Arrendale & Rogers (1981)
	Roofing	19 800-32 500	Malaiyandi et al. (1982)
	Roofing	28 000	Hervin & Emmett (1976)
Fluorene	Electrodes	800-4000	Arrendale & Rogers (1981)
Indeno[1,2,3-cd] pyrene	Not given	Detected	Lang et al. (1959)
	Roofing	Not detected-2460	Malaiyandi et al. (1982)
	Roofing	7300-9300	Wallcave et al. (1971)
Perylene	Roofing	2090-5840	Malaiyandi et al. (1982)
Phenanthrene	Not given	5.4	Gorman & Liss (1985)
	Electrodes	7500-40 300	Arrendale & Rogers (1981)
Pyrene	Not given	14.3	Gorman & Liss (1984)
	Electrodes	4500-34 900	Arrendale & Rogers (1981)
	Roofing	17 500-23 600	Malaiyandi et al. (1982)
	Roofing	20 000	Hervin & Emmett (1976)
Total PAH content	Roofing	265 000-500 000	Malaiyandi et al. (1982)

* From IARC (1985)

1.2.2 Coal Tar Pitch

Coal tar pitch is a dark brown-black, shiny, amorphous residue produced in the distillation of coal tars. This contains PAHs and their methyl and polymethyl derivatives as well as heteronuclear compounds. It has a specific gravity of approximately 1.25 and is a solid at normal temperatures. It may be classified into three grades: soft pitch with a softening point between 25 and 55° C; medium-soft pitch with a softening point between 55 and 75° C; and hard pitch with a softening point above 75° C.

1.2.3 Creosote

The distillate fractions or tar oils obtained by the fractional distillation of crude coal tars are commonly known as creosote. They are fractions or blends of fractions specifically used in timber preservation.

The high boiling distillate fractions of high temperature coal tars include naphthalene oil, creosote oil and anthracene oil. Creosote varies in its composition but consists of aromatic hydrocarbons such as anthracene, naphthalene and phenanthrene, tar acids such as phenol, cresols and xylenols, and tar bases such as pyridine and lutidine.

The major components of some creosotes have been reported by several sources. These data are presented in Table I - 6.

Table I - 6. Major components of some creosotes*

Component	Creosote				
	A**	B***	C****	D#	E##
Acenaphthene	9.0	14.7	3.1	9.0	-
Anthracene	2.0	###		1.5	7.0
Benz[a]anthracene	-	-	-	-	0.16-0.26
Benzo[a]pyrene	-	-	-	-	0.04-0.06
Benzofluorenes	2.0	1.0	-	-	-
Biphenyl	0.8	1.6	-	1.0	-
Carbazole	2.0	1.2	2.4	-	-
Chrysene	3.0	2.6	-	-	-
Dibenz[a,h] anthracene	-	-	-	-	0.01-0.04
Dibenzofuran	5.0	7.5	1.1	4.0	-
9,10-Dihydro-anthracene	-	-	0.2	-	-
Dimethylnaphthalenes	2.0	2.3	-	-	-
Fluoranthene	10.0	7.6	3.4	3.0	0.49-0.93
Fluorene	10.0	7.3	3.1	9.0	-
Methylanthracenes	4.0	3.9####	-	-	-
Methylfluorenes	3.0	2.3	-	-	-
1-Methylnaphthalene	0.9	1.7	3.0+	12+	-
2-Methylnaphthalene	1.2	2.8	3.0+	12+	-
Methylphenanthrenes	3.0	++	-	-	-
Naphthalene	3.0	1.3	15.8	18.0	-
Pyrene	8.5	7.0	2.2	1.0	-

* From IARC (1985)

** Probably a creosote [classes 3,4,5 and 6]; results of replicate runs were within ±0.7% (Lorenz & Gjovik, 1972)

*** Creosote [classes 3,4,5 and 6]; results of replicate runs were within ±0.7% (Lorenz & Gjovik, 1972)

**** Data are averages of nine creosote samples (class 3) (Stasse, 1954; Nestler, 1974)

Typical creosote [classes 3,4,5 and 6] used as a wood preservative for the impregnation of railway sleepers (Andersson et al., 1983)

Range from three different creosotes for wood impregnation [classes 3,4 and 5] (Lehmann et al., 1984)

Data included under phenanthrene

Data include methylphenanthrenes

\+ Methylnaphthalenes

++ Data included under methylanthracenes

+++ Data include anthracene

1.2.4 Coke Oven Emissions

Coke is a porous, cellular carbon residue produced from the destructive distillation of bituminous coal. The major application of coke is in the production of steel. Human exposure to coke oven emissions occurs as a result of chemically-complex emissions released during the distillation process of bituminous coal.

There are three basic reactions that take place during coking, roughly occurring at the following temperatures (IARC 1984):

1. The breakdown products of coal (less than 700° C) are water, carbon monoxide, carbon dioxide, hydrogen sulfide, olefins, paraffins, hydroaromatics and phenolic and nitrogen-containing compounds.
2. Thermal reactions of these products at 700°C produce aromatic hydrocarbons and methane, evolve large amounts of hydrogen and decompose the nitrogen-containing compounds to hydrogen cyanide, ammonia and nitrogen.
3. The production of hard coke is accomplished through the removal of hydrogen (above 700°C).

Much attention has been given to the toxic effects of the particulate phase of the coal tar pitch volatiles (CTPV) emitted

from coke ovens because this fraction contains polycyclic aromatic hydrocarbons (PAH). A partial list of toxic constituents found in the coke oven emissions is given in Table I-7.

1.2.5 Asphalt and Bitumens

Asphalt is a dark brown to black cement-like material in which the predominating constituents are bitumens that occur in nature or are obtained in petroleum processing. It contains very high molecular weight hydrocarbons called asphaltenes and is soluble in oil, turpentine, petroleum, carbon disulphide; insoluble in water, alcohol and acids. It has a specific gravity of 0.95-1.1, a boiling point of less than 470°C, and an ignition temperature of 485° C.

Before 1907, the major portion of asphalt used occurred naturally as native asphalts, rock asphalts and lake asphalts; since that time most asphalts have been produced from the refining of petroleum. The native asphalts include a variety of reddish brown to black materials of semi-solid, viscous-to-brittle character. They may occur in relatively pure form, with 92 to 97% soluble in carbon disulfide and only 3 to 8% mineral content.

Rock asphalt deposits may contain from 5 to 25% asphalt, and may vary from a soft-flux material to hard penetration. The mineral content, usually of a sandstone or limestone nature, has many gradations.

TABLE I - 7
Partial List of Constituents
of Coke Oven Emissions

POLYNUCLEAR AROMATIC HYDROCARBONS

Anthanthrene	Dihydromethyltriphenylene
Anthracene	Dihydrophenanthrene
Benzidene	Dihydropyrene
* Benz(a)anthracene	Dihydrotriphenylene
** Benzo(b)fluoranthene	Dimethylbenzo(b)fluoranthene
** Benzo(ghi)fluoranthene	Dimethylbenzo(k)fluoranthene
** Benzo(j)fluoranthene	Dimethylbenzo(a)pyrene
** Benzo(k)fluoranthene	Dimethylchrysene
Benzofluorene	Dimethyltriphenylene
Benzo(a)fluorene	Ethylanthracene
Benzo(b)fluorene	Ethylphenanthrene
Benzo(c)fluorene	Fluoranthene
** Benzophenanthrene	Fluorene
Benzo(ghi)perylene	* Indeno (1,2,3-cd)pyrene
*** Benzo(a)pyrene	Methylanthracene
* Benzo(e)pyrene	Methylbenz(a)anthracene
Benzoquinoline	Methylbenzo(a)pyrene
* Chrysene	Methylbenzo(ghi)perylene
Coronene	** Methylchrysene
** Dibenz(ah)anthracene	* Methylfluoranthene
** Dibenzo(ah)pyrene	Methylfluorene
Dihydroanthracene	Methylphenanthrene
Dihydrobenzo(a)fluorene	Methylpyrene
Dihydrpbenzo(b)fluorene	Methyltriphenylene
Dihyhdrobenzo(c)fluorene	Octahydroanthracene
Dihydrobenz(a)anthracene	Octahydrofluoranthene
Dihydrochrysene	Octahydrophenanthrene
Dihydrofluoranthene	Octahydropyrene
Dihydrofluorene	Perylene
Dihydromethylbenz(a)anthracene	Phenanthrene
Dihydromethylbenzo(K and b) fluoranthenes	O-Phenylenepyrene
Dihydromethylbenzo (a and e) pyrenes	Pyrene
Dihydromethylchrysene	Triphenylene

Cont'd

Table I-7
Cont'd...page 2

POLYNUCLEAR AZA - HETEROCYCLIC COMPOUNDS		TRACE ELEMENTS	
	Acridine	***	Arsenic
**	Benz(c)acridine		Beryllium
**	Dibenz(a,h)acridine	***	Cadmium
**	Dibenz(a,j)acridine	***	Chromium
			Cobalt
	AROMATIC AMINES		Iron
			Lead
***	B-naphthylamine	***	Nickel
	a-Naphthylamine		Selenium
	OTHER AROMATIC COMPOUNDS		OTHER GASES
***	Benzene		Ammonia
	Phenol		Carbon disulfide
	Toluene		Carbon monoxide
	Xylene		Hydrogen cyanide
			Hydrogen sulfide
			Methane
			Nitric oxide
			Sulphur dioxide

Source: Ministry of Labour, Occupational Health Branch 1982
**** - proven human carcinogens
*** - suspect human carcinogens
** - animal carcinogens (strong or moderate)
* - animal carcinogens (weak)

Lake asphalt exists in a number of deposits on the island of Trinidad, near the northeast coast of Venezuela. Trinidad asphalt has a relatively uniform composition of 29% water and gas, 39% bitumen soluble in carbon disulfide, 27% mineral matter on ignition, and 5% adsorbed on the mineral matter. (Evans 1983).

The terms bitumen' and asphaltic bitumen' are used in Europe and are synonymous with the term asphalt' used in North America. The term bitumens refers to products derived from residues resulting from the vacuum distillation of selected petroleum crude oils. They are widely used for paving, roofing and industrial applications. A clear distinction must be made between coal tars and their products which are the result of the destructive distillation of coal, and coal tar pitches which are residues derived from the distillation of coal tars. This crucial distinction must be made in some applications. Mixed exposures may be encountered such as in roofing.

The chemical composition of bitumens may vary depending both on the original crude oil and on the process used during refining. Bitumens generally are complex mixtures containing a large number of different chemical compounds of relatively high molecular weight: typically, 82-85% combined carbon, 12-15% hydrogen, 2-8% sulphur, 0-3% nitrogen and 0.2% oxygen. Bitumens contain predominantly cyclic hydrocarbons (aromatic and/or naphthenic) and a lesser quantity of saturated components, which, because of the slow and lengthy processing at moderate

temperatures, are mainly of very low chemical reactivity (IARC 1985).

Polynuclear aromatic hydrocarbons (PAHs) are present in bitumens. The levels of PAHs analysed in various bitumens are shown in Table I - 8.

1.2.6 Petroleum Pitch

Petroleum pitches are dark colored bituminous substances obtained as non-volatile residues from destructive distillation processes carried out during the refining of petroleum. For the purposes of this report these definitions will be used to maintain consistency.

Table I - 9 is a partial classification of the bituminous materials that have been described in this chapter.

Table I - 8. Content of polynuclear aromatic hydrocarbons (PAHs) (mg/kg) in eight different bitumen samples*

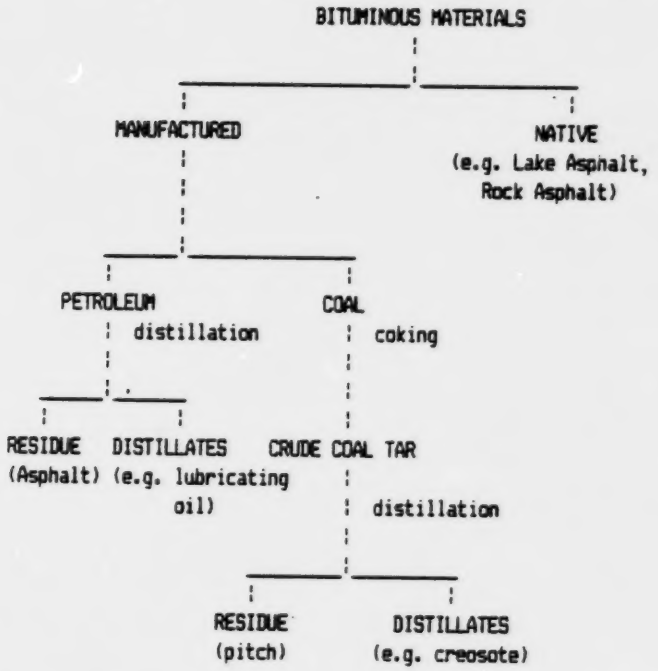
PAH	Formula	Bitumen**							
		A	B	C	D	E	F	G	H
Anthracene	C14H10	ND	ND	ND	ND	ND	ND	ND	ND
Phenanthrene	C14H10	2.3	0.4	3.5	1.3	0.6	35#	1.1	2.3#
Pyrene	C16H10	0.6	1.8	4.0	8.3	0.9	38	0.3	0.08
Fluoranthene	C16H10	+	+	2.0-	+	+	5	ND	ND
Bnezofluorenes	C17H10	+	+	+	+	+	+	+	ND
Benz[a]anthracene	C18H12	0.15	2.1	1.1	0.7	0.9	35	0.2	ND
Triphenylene	C18H12	0.25	6.1	3.1	3.4	3.8	7.6	1.0	0.3
Chrysene	C18H12	0.2	8.9	2.3	3.9	3.2	34	0.7	0.04
Benzo[a]pyrene	C20H12	0.5	1.7	1.3	2.5	1.6	27	0.1	ND
Benzo[e]pyrene	C20H12	3.8	13	2.9	3.2	6.5	52	1.6	0.03
Benzo[k]fluoranthene	C20H12	+	ND	+	-	+	ND	ND	ND
Perylene	C20H12	ND	39	2.2	6.1	2.9	3.0	0.1	ND
Anthanthrene	C22H12	ND	Tr	Tr	Tr	+	1.8	ND	ND
Benzo[ghi]-perylene	C22H12	2.1	4.6	1.0	1.7	2.7	15	0.6	Tr
Indeno[1,2,3-cd]pyrene	C22H12	Tr	ND	Tr	Tr	Tr	1.0	ND	ND
Picene	C22H12	+	+	+	+	+	1.0	+	ND
Coronene	C24H12	1.9	0.8	0.5	0.2	0.9	2.8	0.9	ND

* From IARC (1985)

** ND, not detected; #, estimate includes alkyl derivatives;

+ not estimated but present in small amount; Tr, trace

Table I - 9. Partial classification of bituminous materials*



*Adapted from U.S. EPA (1978)

1.3. Historical Perspectives

Experimental work by Percival Pott on the causes of human cancer developed from the observation that workers in certain occupations which were known to be associated with exposure to soot or to coal tar products had an increased risk of developing cancer of the skin. This was the first instance in which it appeared that a cause of cancer could be identified and it resulted in extensive research in the early 1900s in an attempt to identify the substance or group of substances that might be the responsible agents. It is of some interest to note that even at this time it was claimed that workers in equivalent industries but in different countries appeared to be at substantially different risk. For example, skin cancer was common in coal tar pitch workers in Britain but this condition was claimed to be extremely rare in similar workers in France, Woglom (1926). While such differences might be due to different work practices or to very different working conditions there was also a possibility that it could be due to some chemical differences associated with the industrial process. This is an important early example of the care that is required in transferring risk estimates from one industrial situation to another unless precautions are taken to standardize for exposure to the appropriate etiological agents.

These early observations stimulated an intensive search for the identification of the chemicals which were present in tar or

soot and experiments were designed to try to induce cancer in animals by repeated painting of the skin with tar or soot. It was assumed that repeated skin contact by various chemicals was the causative mechanism of human skin cancer and it appeared logical to repeat the process in the experimental animal model.

Unfortunately it was not realized at the time that there are important differences in the susceptibility of animals to the development of skin cancer. Research groups carried out extensive experiments using very large numbers of animals and consistently reported negative results. This paradox remained unexplained until Japanese workers had the good fortune to choose, by chance, a susceptible species and to continue painting the skin for the very prolonged period of time that is now known to be required. Yamagiwa and Itchikawa (1914) finally reported that skin cancer could be caused in mice by repeated painting with tar. This original paper has become one of the classic contributions in the field of cancer research.

It rapidly became obvious that the cancer was due to some specific chemical or substances in the tar and was not due to a simple irritant effect. This was an important contribution since tar painting caused chronic inflammatory changes and it was important to demonstrate that the persistent inflammation was not itself a cause of cancer. Many other substances such as alkalies or acids were well known to cause chronic irritation or inflammation but these changes were not, in themselves, sufficient to cause malignant change. Following the discovery by Yamagiwa

and Itchikawa that there was something specific about the ability of tar products to cause cancer, the next step was the problem of identifying the particular causative chemicals. It is worth emphasizing that nobody at the time believed it likely that a single chemical was involved (Woglom 1926), even though, as will be noted below, attention gradually became focussed during the next few years on one substance.

The difficulty of sorting out the cancer causing agents in coal tar was due to the fact that it appeared to contain several hundred substances in various concentrations and only about 100 of these had been identified by Woglom (1926). During the industrial production of coal tar the material was normally separated by distillation into 4 or 6 fractions of differing boiling points. The various research groups carefully tested each of these various fractions for carcinogenic potential by means of animal skin testing. The most important fraction appeared to be that which was distilled at temperatures greater than 200°C. A number of different compounds were identified, either because they were present in relatively high concentrations, or because they gave rise to specific chemical compounds which could be fairly easily analyzed. However, none of these appeared to cause cancer when tested on animals in the way that had been obtained with the parent tar. Increasingly it appeared that the agents responsible for cancer might be highly specific and might be causing their effect despite being present in exceedingly low concentrations.

The analytical problems were formidable until Hieger (1930) at the Cancer Research Institute in London observed that certain tars and oils, in addition to being capable of causing skin cancer, also showed intense fluorescence when exposed to ultraviolet light. Finally, Cook et al. (1933) isolated the fluorescent material from the distillate of coal tar and found that this was largely due to 1:2 benzopyrene. They also found this chemical to be highly carcinogenic. They concluded that this chemical was certainly one of the potent substances in tar to which its carcinogenic properties could be attributed. The fortuitous properties of 1:2 benzopyrene which makes it fluoresce in ultraviolet light and which also happens to account for its carcinogenic potential greatly assisted research and also, to some extent, accounted for the increasing attention that was subsequently given to this chemical. Since it was now known that coal tar when heated to an appropriate temperature produced carcinogens, many other materials were also heated to above 700° F. These included isoprene, acetylene, human skin and muscle and all of these were found to produce carcinogens but of unknown identity (Kennaway 1930).

Research interest at this time shifted to the study of synthetic carcinogens and the probability that other carcinogens were present in tar does not appear to have been followed up. It seems to have been assumed that 1:2 benzopyrene was the only carcinogen in tar despite the fact that the response to tar painting in animals was very different from that caused by the

application of pure 1:2 benzopyrene. Berenblum and Schoental (1947) decided to study this problem and were able to show that tar from which all the 1:2 benzopyrene had been extracted still had strong carcinogenic potential. They were not, however, able to identify the nature of the substances.

CHAPTER TWO

PHARMACOKINETICS

2.1 Absorption, Distribution, Biotransformation, and Excretion of Polycyclic Aromatic Hydrocarbons.

Little information on the pharmacokinetics of specific types of complex mixtures could be found in the literature. Most investigations dealt with the constituents of interest, namely polycyclic aromatic hydrocarbons. Therefore, the following section focuses on these types of substances only and inference can be drawn to the different types of products considered overall in the document.

2.1.1 Absorption

The major routes of occupational exposure to polycyclic aromatic hydrocarbons are through the lungs by inhalation of aerosols and/or hydrocarbon-adsorbed particles and through the skin by direct contact with the hydrocarbons.

Absorption of PAHs across the pulmonary endothelium has been studied through inhalation studies of pure aerosols and after intratracheal administration of hydrocarbons adsorbed on particles of various sizes and chemical compositions. Clearance studies of PAHs from the lungs have not generally differentiated

between systemic absorption through pulmonary tissues and removal of hydrocarbons by mucociliary clearance. The clearance of carbon particles and the simultaneous rate of elimination of benzo[a]pyrene (BaP) from the respiratory tract was measured. BaP adsorbed to 15 to 30 µm carbon particles was eliminated from the lung at essentially the same rate as the carbon particles were cleared. In contrast BaP adsorbed onto 0.5 to 1.0 µm carbon particles was eliminated from the lung approximately 4 times faster than the carbon particles were cleared (Creasia et al. 1976). In rats, after inhalation of tritiated benzo[a]pyrene (^{3}H-BaP; 500 µg/l; activity mass median diameter, 1-2 µm) for 1 hr, significant amounts of radioactivity were found in the nasal turbinates, trachea, larynx, lungs, tracheobronchial lymph nodes, kidneys and liver immediately after exposure. Benzo[a]pyrene inhaled in this particulate form was rapidly solubilized, translocated to internal organs and excreted primarily in feces (Mitchell, 1982).

The regional deposition clearance rate from the respiratory tract is dependent on the size and chemical composition of the particle as well as the structure of the hydrocarbon. Nagel et al. (1976) compared the morphologic effects and the retention and distribution times of single and multiple intratracheal instillations in Syrian hamsters of 7H-dibenzo[c,g]carbazole (DBC) and benzo[a]pyrene (BaP). A single instillation of DBC induced slight changes in the hamster respiratory tract; however, the treatments caused

tracheobronchial epithelial proliferation, cell hyperplasia, and occasionally squamous metaplasia. The particle size of both carcinogens was approximately the same. BaP in saline remained longer in the lungs longer than did DBC in saline. The shortest retention time was recorded when single doses of DBC were administered in aqueous solution, whereas multiple doses of DBC in aqueous solution did not markedly affect retention time. DBC passed from the lungs to the intestinal tract and was mainly excreted in the feces. The pulmonary absorption has further been explored by comparisons of administration either through the lungs by inhalation or through the gastrointestinal tract by gavage (Vainio, 1976).

Mitchell and Tu (1979) measured pyrene in tissues of Fischer 344 rats at different times after inhalation of pyrene aerosols (500 µg/l; mass median diameter, 0.3-0.8 µm) for 1 hr. Significant quantities of pyrene were found in nasal turbinates, trachea, lungs, kidney, and liver immediately after exposure. Clearance from the respiratory tract was rapid; concentrations in the trachea and lungs 48 hrs after exposure were 20 and 5% respectively of the concentrations present 1/2 hour after exposure. Pyrene also cleared from liver and kidney at a relatively rapid rate; concentrations in these tissues 48 hrs after exposure were approximately 10% of those 1/2 hr after exposure. Concentrations in the gastrointestinal tract 24 hrs after exposure were 4 times those found 1/2 hr after exposure. Thus, inhaled pyrene is rapidly cleared from the respiratory

tract by mucociliary action from the trachea and bronchi and by translocation from the respiratory tract to the liver and kidney; it is eliminated primarily through the gastrointestinal tract.

Skin absorption has been studied by tracer studies of benzo[a]pyrene (Heidelberger and Weiss, 1951). Radioactivity following intravenous injections of labelled benzpyrene-5-C was found to be recovered quantitatively. No radioactivity appeared in the expired CO_2. The compound and its metabolites were rapidly excreted into the bile, gastrointestinal tract, and feces. There was significant absorption into body fat. The half-time of disappearance of radioactivity from benzpyrene-5-C from the site of subcutaneous injection in tricaprylin was 1 and 3/4 weeks, and excretion took place through the feces. The rate of disappearance of radioactivity from the site of a single application of benzpyrene-5-C had two phases, the half-times of which were approximately 1 and 2/3 days and 4 and 1/3 days.

2.1.2 Distribution

Once absorbed polycyclic aromatic hydrocarbons once absorbed are rapidly distributed throughout the body via the blood stream. A number of studies by Heidelberger and Weiss (1951), Kotin et al., (1959) and Mitchell (1982) indicate that detectable levels of hydrocarbons can be observed in most internal organs from minutes to hours after administration. Mammary and other fat tissues are significant storage depots where hydrocarbons may

accumulate and slowly be released. The gut contains relatively high levels of hydrocarbons or hydrocarbon metabolites as a result of hepatobiliary excretion of metabolites or swallowing of unmetabolized hydrocarbons following mucociliary clearance after inhalation exposure.

PAHs have been observed to be related to toxicity and carcinogenicity in fetuses and offspring of maternally-exposed animals (Tomatis, 1973). Certain PAH's can readily cross the placenta of intragastrically-dosed rats (Shendrikova and Aleksandrov, 1975). In guinea pig models, intravenous doses of benzo[a]pyrene which has been labelled, readily cross to the fetus (Kelman and Springer, 1982).

2.1.3 Metabolism

The NADPH-dependent cytochrome P-450 monooxygenase system is the most important producer of oxidative, reductive or hydrolytic reactions which exist in a number of forms with different overlapping substrate specificities (Conney, 1982). Many PAHs that are metabolized by cytochrome P-450 monooxygenases are inducers of this enzyme system as well. This effect may in fact increase or decrease the toxicological response depending on the relative induction clearance rates of the toxic metabolites .

Many studies have been carried out on benzo[a]pyrene as a model for PAH metabolism. These have been reviewed extensively

in a number of publications by Sims and Grover (1974); Selkirk (1977); Conney (1982); Levin et al (1982); Cooper et al., (1983).

Benzo[a]pyrene is metabolized initially by the microsomal cytochrome P-450 monooxygenase system to several arene oxides. Once formed, these arene oxides may rearrange spontaneously to phenols, or undergo hydration to the corresponding trans-dihydrodiols in a reaction catalysed by cytosolic glutathione S-transferases. Phenols may also be formed by the cytochrome P-450 monooxygenase system by direct oxygen insertion, although unequivocal proof for this mechanism is lacking. The 6-hydroxy-benzo[a]pyrene is further oxidized either spontaneously or metabolically to the 1,6-, 3,6- or 6,12-hydroquinones, and is also a presumed intermediate in the oxidation of benzo[a]-pyrene to the three quinones catalysed by prostaglandin endo-peroxide synthetase (Marnett et al., 1977, 1979). Evidence exists for the further oxidative metabolism of two additional phenols: 3-hydroxybenzo[a]pyrene is metabolized to the 3,6-hydroquinone, and 9-hydroxybenzo[a]pyrene is oxidized to the K-region 4,5-oxide, which is hydrated to the corresponding 4,5-dihydrodiol. The phenols, hydroquinones and dihydrodiols can all be conjugated to glucuronides and sulphate esters, and the hydroquinones also form glutathione conjugates.

In addition to being conjugated, the dihydrodiols undergo further oxidative metabolism. The cytochrome P-450 monooxygenase system metabolizes benzo[a]pyrene 4,5-dihydrodiol to a number of uncharacterized metabolites, while the 9,10-dihydrodiol is

metabolized predominantly to its 1- and/or 3-phenol derivative, with only minor quantities of a 9,10-diol-7,8-epoxide being formed. In contrast to 9,10-dihydrodiol metabolism, the principal route of oxidative metabolism of benzo[a]pyrene 7,8-dihydrodiol is to a 7,8-diol-9,10-epoxide, and phenol-diol formation is a relatively minor pathway. The diol epoxides can be conjugated with glutathione either spontaneously or by a glutathione S-transferase catalysed reaction. They may also hydrolyse spontaneously to tetraols, although epoxide hydrolase does not catalyse the hydration. Taken together, these reactions illustrate that benzo[a]pyrene, and all hydrocarbons in general, can undergo a multitude of simultaneous and sequential transformations; they underscore the difficulties in determining which metabolites are responsible for the biological effects of the parent hydrocarbon.

An additional complexity in the evaluation of hydrocarbon metabolism is the fact that the compounds are metabolized to optically active products by the stereoselective metabolism of benzo[a]pyrene to its four metabolically possible 7,8-diol-9,10-epoxides. A total of four isomers are possible, since each diastereoisomer can be resolved into two enantiomers. With rat liver microsomes, the (+)-[7R,8S]oxide of benzo[a]pyrene is formed in a 20-fold excess relative to the (-)-[7S,8R]-isomer and is metabolized stereospecifically by epoxide hydrolase to the (+)-[7R,8R]-dihydrodiol (Thakker et al., 1977). More than 90% of the benzo[a]pyrene 7,8-oxide formed consists of the

(+)-[7R,8S]-enantiomer (Levin et al., 1982). This metabolically predominant dihydrodiol is metabolized primarily to a single diol epoxide isomer, (+) benzo[a]pyrene 7,8-diol-9,10-epoxide-2[7R,8S,9S,10R]. The biological significance of stereoselective formation of the 7,8-diol-9,10 epoxide isomers is that the metabolically predominant isomer is also the only isomer with high tumorigenic activity, and it is the predominant isomer found covalently bound to DNA in a variety of mammalian cells and organs exposed to benzo[a]pyrene.

The current interest in diol epoxides as ultimate carcinogens stems from the initial observation by Sims et al., (1974) that a 7,8-diol-9,10-epoxide is the intrinsically active metabolite responsible for the covalent binding of benzo[a]pyrene to DNA. It remains to be determined whether diol epoxides are the general metabolically activated forms of PAH. If this is the case, it is also important to determine which diol epoxide(s) mediate the biological activity, since many PAHs can form more than one diol epoxide. The unique structural features of the diol epoxide metabolite were proposed on the basis of structure--activity relationships of benzo[a]pyrene epoxides, a re-evaluation of published tumorigenicity data and the quantum mechanical calculations of Jerina et al., (1976). It was predicted that benzo-ring diol epoxides, in which the epoxide forms part of the bay region of the hydrocarbon molecule, should have high chemical reactivity, high biological activity and, if metabolically formed, would be likely candidates as ultimate

carcinogenic metabolites of PAHs. A bay region occurs in a PAH when an angularly-fused benzo-ring is present; for example, the sterically-hindered region between the 10- and 11-positions constitutes the bay region of benzo[a]pyrene. To date mutagenicity, DNA binding, cell transformation, metabolism and tumorigenicity studies have indicated that bay-region diol epoxides of about a dozen PAHs are ultimate carcinogenic metabolites. Furthermore, metabolic studies with hydrocarbons such as benzo[a]pyrene by MacLeod et al., (1979); Wood et al., (1979); MacLeod et al., (1980); Thakker et al., (1981) have indicated that minimal metabolic formation of the bay-region diol epoxide is consistent with the weak biological activity of the parent hydrocarbon.

It should be emphasized that the demonstration of high biological activity of a metabolically formed bay-region diol epoxide does not preclude the existence of other ultimately carcinogenic metabolites of PAHs, and that not all carcinogenic hydrocarbons have formal bay regions.

Considering the fetal metabolism of PAHs, it is important to recognize that the development of metabolic enzymes occurs rather late in fetal development. They can be induced to develop earlier by exposure to appropriate substrates although usually to a lesser degree than in adults (Tomatis, 1974).

2.1.4 Excretion

Once metabolized, portobiliary excretion and elimination through feces is the major route by which PAH's are removed from the body (Kotin 1959; Chipman 1982). It is important to note that metabolism rather than biliary transport is the rate-determining step in the biliary excretion of benzo[a]pyrene (Schlede et al., 1970).

2.2 Summary - Pharmacokinetics

The available evidence indicates that complex mixtures of polycyclic aromatic hydrocarbons are absorbed primarily through inhalation and cutaneous exposure. Some gastro-intestinal absorption occurs, primarily as a result of mucociliary clearance of inhaled non-respirable particles. Metabolic studies using benzo[a]pyrene as a model show metabolism and biotransformation through the cytochrome P-450 system with products such as diol-epoxides as the ultimate carcinogens derived from the PAHs. The presence of a formal bay region diol-epoxide strongly suggests but does not preclude the existence of other ultimately carcinogenic metabolites of PAH's and not all carcinogenic hydrocarbons have formal bay regions. The major route of excretion is through the liver, biliary tract and feces.

CHAPTER THREE

ACUTE AND CHRONIC TOXIC EFFECTS

3.1 Experimental Animal Studies

The following section describes the available evidence relating acute and chronic toxic health effects of exposures to the various mixtures of concern.

3.1.1 Coal Tar Products

Libke and Davis (1967, 1968) did a series of animal studies using powdered clay pigeon targets, the main ingredient of which was coal tar pitch. In feeding studies, young pigs who were four to nine weeks old, were fed a standard 14% protein ration ad libitum. Ground clay pigeon material was fed at 15 gm per pig per day for the first 2 days; and beginning on the third day, at 30 gm per pig per day. The pigs developed severe hepatic centrilobular necrosis and hemorrhage, often fatal, with related hematologic changes. Goat feeding studies produced non-hemorrhagic hepatic lesions and weight loss in all animals when 1,350, 750, 675 and 675 gm of clay pigeon material were given to the four animals respectively. Carlton (1966) fed clay pigeons to Peking ducklings and found dose-related gross abnormalities with microscopic liver changes. Kudrin (1968) studied

the toxicity of pitch tar varnish used for the waterproofing of logs transported in rivers and reservoirs used as sources of drinking water. Rats were given daily oral doses of 10 mg/kg or 100 mg/kg. In a three month study, there were no changes in behaviour, nervous system function and biochemistry in the low dose group. In the high dose group, weight gain declined in the second month and pathological changes in unspecified organs occurred. The varnish was considered harmless at a concentration of 5 mg/kg with a maximum permissible limit of 10 mg/kg.

Emmett et al. (1977) studied the effect on rabbit eyes of roofing coal tar pitch volatiles prepared by collecting vapours from a large sample maintained at 200° C. Installation of 10 microlitres of this distillate into the conjunctivae of rabbits maintained in UV-free quarters produced only minimal or temporary irritation. Irradiation with long-UV light (330-380 nm) at 2.0 x 10^2 joules/m^2 shortly after conjunctival installation produced marked photophobia and severe kerato-conjunctivitis. Mills (1978) showed that ultra-violet radiation enhanced the comedogenicity of sebum and various exogenous substances. He also exposed the ears of rabbits to various substances including 1% crude coal tar in petrolatum. Ultra- violet radiation using a 1600 W solar lamp was used. He found the addition of the solar stimulation enhanced the degree of follicular hyperkeratosis.

Tonogai et al., (1980) explored the toxicity of coal tar dyes on fish. It was found that when coal tar dyes were treated with sodium hypochlorite, chloroform was detected in the dye

solution. Chloroform and its homologous compound had serious effects on the fish. He also found that xanthene dyes under photo radiation resuled in the excited triplet state and halogen in the dye molecule was liberated in free form.

McKee et al., (1984) examined the acute toxicity of a series of potential streams from the EDS coal liquefaction process. The EDS (Exxon Donar Solvent) process is a modern coal liquefaction technology developed in New Jersey, U.S.A. McGee found some evidence of ocular and dermal irritation after exposing New Zealand white rabbits. This effect was particularly related to the phenolic content of the substances. These phenolic compounds are often present in high concentrations in coal tar fractions boiling below coal tar pitch, for example anthracene and creosote oil. Such fractions are toxic and may cause high mortality when administered repeatedly, as in some studies of carcinogenicity. Some phenols may act as co-carcinogens as reported by Boutwell and Bosch (1959). Phenols are present in only small amounts in tar pitch, but may occur in toxic concentrations in heavy tars or soft pitches which contain considerable amounts of material with lower boiling points.

A summary of the acute and chronic effects of coal tar and derived products in animal studies is tabulated in Table III - 1.

Table III - 1 Summary of the Acute and Chronic Effects of Coal Tar and Derived Products in Animal Studies

Author/year	Exposed to	Exposure Route, Concentration and Duration	Species	No. of Animals	Effects/Outcomes
Kudrin 1968	Pitch Tar Varnish	Daily doses orally of 10mg/kg or 100 mg/kg in a 3 month study	Male Wistar Rats		No changes in behaviour nervous system function biochemistry in/on dose group Weight gain declined in the second month and pathological changes in unspecified organs occurred in high dose group.
Kovalenko 1965	Bituminous Coal Pitch	Injection into the sebaceous glands	Rats		Inflammatory epithelial proliferation, with stratified squamous epithelium.
Emmett et al. 1977	Coal Tar Pitch Volatiles	10 microlitres of the distillate to both eyes	Rabbits		Marked photophobia and severe kerato-conjunctivis
Mills 1978	Crude Coal Tar	1% crude coal tar in petrolatum, applied daily for 5 weekdays for 2 weeks, ultra-violet radiation using a 1600 w solar lamp	Rabbits	5	The addition of the solar stimulation enhanced the degree of follicular hyperkeratosis

cont'd

Table III - 1
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Tonogai et al. 1980	Coal Tar Dyes	In one solution, pH 7.0 containing 3,000 mg/L of a dye to be tested, without direct sunlight from 48 hrs, water temperature was 25 deg C. In another solution, one liter of dye containing 200 mg/L of Phloxine (pH 6.8) and 100 mg/L of Rose Benzale (pH 6.9), were irradiated with 150 W white light from above 20 cm of the water level	Fish	10	Coal tar dyes treated with sodium hypochlorite, chloroform was detected from the dye solution, exhibiting a strong acute toxicity to fish
McKee et al. 1984	Coal Liquefaction	A single 0.1 g or 0.1 ml dose was installed into the lower conjunctival cul de sac of the left eye of the animal at regular intervals throughout a 14-day observation	Rabbits	9	Minimal acute toxic hazards hazards and evidence of ocular and dermal irritation

3.1.2 Bitumens

Wallcave et al., (1971) studied the skin effects of exposure to samples of eight different bitumens. Random-bred Swiss albino mice were given twice weekly applications of 25 microlitres of bitumen in a 10% benzene solution to shaved areas of the back for an average of 81 weeks. Inflammatory infiltration of the dermis and cutaneous ulceration with abscess formation was found with epidermal hyperplasia generally. Amyloidosis of the spleen and kidney was also observed.

Inhalation exposure studies of Hueper and Payne (1960), and Simmers (1964) observed the effects of aerosols and smoke of bitumens on guinea pigs, rats, and mice. Effects included patchy regions of emphysema, bronchiolar dilation, pneumonitis and severe local bronchitis.

3.2 Experimental Exposure of Humans.

3.2.1 Coal Tar Products

The first experimental evidence that coal tar pitch was a photo-sensitizing agent was described by Foerster and Schwartz (1939). This followed an initial report by Lewin (1913) describing a series of patients exhibiting photo-toxic reactions to coal tar and light. This effect was also reported most notably by Goeckerman (1929), and Herrik and Sheard (1928).

Foerster and Schwartz (1939) conducted patch tests on the skin of pitch workers and controls under various physiological conditions using pitch and a variety of solvents. Their results showed that in most subjects pitch elicits photo-toxic reactions to light with wave-lengths from 390 to 500 nm. No reactions were seen to UV light of less than 250 nm or to infrared light. Sunlight filtered through window glass did elicit a photo-toxic response. Patch areas washed before irradiation still showed typical pitch photosensitization. They also reported responses to anthracene, acridine and phenanthrene but stated that none of these compounds alone was responsible for the photo-toxicity of pitch.

Crow et al., (1961) patch-tested workers with pitch dissolved in chloroform. Most subjects complained of "pitch smarts" when exposed to light from 340 to 430 nm. The response in these workers was similar to pitch photo-toxicity seen in the field. Reactivity of a patch-tested area remained for several weeks rather than several days. They found that anthracene, but not acridine, regularly caused photo-toxic reactions in patch tests with light from 340 to 380 nm. Kaidbey and Kligman (1977) reported that anthracene, fluoranthene and phenanthrene were as photo-toxic as coal tar.

Experiments by Everett et al., (1961) showed that coal tar derivatives applied before exposure did not elicit these types of responses except when irradiation was between 350 to 400 nm. Wulf et al., (1963) in a total of 7,288 individual patch tests on

105 test persons found that only certain constituents of coal tar were distinctly photo-dynamic. This confirmed the hypothesis of Burckhardt that high-boiling fractions in coal tar are photo-dynamically active, including anthracene, pyrene, fluoranthene and benzo[a]pyrene.

Diette et al., (1983) examined the delayed erythema and skin pain tar smarts by quantifying the amount (dose) of UVA and exposure conditions required to induce these phenomena in normal human skin. The minimal UVA dose required to induce delayed erythema (minimal photo-toxic dose or MPD) and the minimal UVA dose required to induce an immediate smarting reaction (minimal smarting dose or MSD) were recorded in 32 subjects in a variety of settings. A log-log dose response model described the relation between the interval of time tar was left on the skin and the lowering of the MPD period. They examined four different methods of tar removal and showed that several methods of using more than water alone were equally effective judging by resultant phototoxicity. The time between tar removal and UVA radiation is important. Even 30 minutes was sufficient for the MPD to increase from 3.77 (+/-1.55) to 6.1 (+/- 4.0) J/cm^2 ($p < 0.02$). The smarting reaction showed a similar dependence on the time interval between tar removal and exposure. The mean MSD was less than the mean MPD at all times. Both manifestations of coal tar photo-toxicity, reduced delayed erythema threshold and susceptibility to the smarting reaction, persisted at least 30 hours after tar removal.

The nature and molecular basis of these reactions were explored by Pathak and Joshi (1983). The therapeutic and photo-sensitizing actions of crude coal tar were due to the photoconjugation of the photoreactive ingredients of crude coal tar with DNA, causing interstrand cross-links and production of singlet oxygen. This is responsible also for the cell damage and cellular edema.

3.2.2 Asphalt

Truc and Fleig (1913) described ocular lesions, conjunctivitis and ulcerative keratitis induced by dust and vapours of asphalt. It is not clear, however, whether these substances were purely of petroleum origin or whether they included coal tar products.

3.3 Observed Effects Resulting from Occupational and Non-experimental Exposures

3.3.1 Dermatologic Effects

A number of skin changes have been observed following exposure to coal tar products alone or combined with asphalt. Other complicating factors include; effects of sunlight, changes in temperature, and the skin complexion of subjects. Most of the classic detailed descriptions are found in the early literature

from Oliver (1908); Schamberg (1910); Foerster and Schwartz (1939); Henry (1947); Ross (1948); Fisher (1953); Combes (1954); Eckardt (1959); Lev et al., (1966); and Hodgson and Whitely (1970). Recent descriptions include studies by Hervin and Emmett (1976); Emmett et al., (1977); Lavker et al., (1981) and Gorman and Liss (1985). Based on these reports the acute and chronic effects on the skin can be summarized as follows:

1) Tar pitch burns: burns from hot pitch and tar are relatively common and result in epidermal atrophy and may be related to skin cancer.

2) Allergic eczematous dermatitis: allergic reactions occur in occupational exposures but more commonly result from use of coal tar medications.

3) Folliculitis, comedones, acneiform lesions: these common lesions usually occur after one month of exposure and are usually limited to the face, neck and upper limbs. They may also appear on areas such as the thighs which are abraded by clothing. Sebaceous cysts may appear on the scrotum. These lesions are attributed to blockage of follicles with tar and pitch and induced keratin production in the pilosebaceous glands. Spontaneous remission appears when exposure ceases. These effects can be reduced substantially by preventive measures and good personal hygiene.

4) Tar erythema or pitch smarts: crude coal tar and coal tar pitch are photosensitizing or photo-toxic agents.

Combined exposure to dust or fumes from tar and pitch and to sunlight results in a painful and stinging condition characterized by an immediate eruption of wheals and reddening followed by epidermal injury. After several episodes of photo-toxic reactions, chronic hyperpigmentation may occur. The photosensitization reaction usually begins within an hour of exposure to light and pitch and may continue for many hours after exposure. In some cases re-exposure to sunlight in the absence of pitch within the next several days will result in burning. The face, neck and forearms which are usually exposed are most commonly affected. Peeling occurs in three to five days even in the absence of erythema. Exposure to high humidity, sweating and high concentration of fumes, especially from the overheating of pitch, wind and strong sunlight all seem to intensify the photo-toxic reaction.

5) Chronic hyperpigmentation, pitch melanosis: chronic melanosis or darkening of the skin may develop five or more years after exposure to coal tar pitch and may be accompanied by other skin changes. Melanosis may follow repeated photo-toxic episodes and may also affect unexposed areas. Hyperpigmentation occasionally follows chronic pitch exposure and photosensitization.

6) Chronic tar dermatoses or shagreen skin: this condition

is an essentially irreversible process affecting forearms, back of the neck, face and hands and usually requires at least 10 years of exposure. Manifestations may include keratin hydroplasia, effects of repeated photosensitization, telangiectasia, pigment changes, and aplasia.

Recent reports from Gorman and Liss (1985) are of note because of the non-heated nature of the exposure process. Very few reports of clinical effects of exposure to asphalt without coal tar exposure have appeared in the literature. Some cases of dermatitis related to asphalt exposure alone were mentioned by Baylor and Weaver (1968).

The only report of an asphalt effect was from a NIOSH Health Hazard Evaluation in 1974 at Ashland Oil. They found photo-toxic skin reactions in the asphalt refinery where there was exposure to polycyclic aromatic hydrocarbons. Photosensitivity reactions affected the outdoor workmen handling these petroleum-based products. It was found that the skin of Blacks and Indians with their increased pigmentation, had some definite protective value. The analysis of petroleum pitch revealed phenanthrene and other closely related compounds.

3.3.2 Ocular effects.

Acute and chronic eye symptoms from exposure to pitch have been reported by Moret (1912); Foerster and Schwartz (1939);

Fisher (1953); Barkov and Prosetskii (1958); Crow (1961); Lev (1966); Susorov (1970); Hervin and Emmett (1976); Emmett (1977); Gorman and Liss (1985). The product was obtained by distilling tar, and was a hard blackish material, composed of the heavy oils of tar (carbolic acid), of solid hydrocarbons, and of carbons.

Acute episodes of eye involvement from either coal tar pitch fumes or pitch dust usually begin 2 to 4 hours after the initial exposure or beginning of the work shift. Symptoms may include reddening of the eyelids and conjunctiva sometimes accompanied by distorted vision and swelling and spasms of the eyelids. After the exposure has stopped symptoms continue to increase. Within about 12 hours the eyes may be matted shut with discharge. In mild cases symptoms disappear within 3 days although photophobia may continue for 1 to 2 months in the absence of further pitch exposure. Attempts to reduce the severity of the response may include wearing protective eye glasses or working at night. Prolonged exposure to pitch dust or volatiles may result in chronic conjunctivitis and corneal staining with reduction in dark adaptation. This may lead to corneal anesthesia and restriction of visual fields and pterygium.

3.3.3. Respiratory Effects

Exposure to coal tar pitch dusts has been noted to result in acute upper respiratory distress such as nasal congestion, hoarseness, throat irritation and swelling. Coughing was

reported by Susorov (1970) and Lev (1966). Respiratory symptoms including bronchitis, chronic cough, nose and throat inflammation and congestion were described by Zeglio (1950) in workers exposed to native asphalt, possibly adulterated with pitch.

Walker et al., (1971) examined 881 men in two coking plants in the U.K. Among 169 workers, 148 of whom were smokers, 80 of 334 oven men had bronchitis (by questionnaire and lung function test), compared with 89 of 547 other coke workers. Smoking alone, together with dusty work, appear to be causative factors for bronchitis in coke-production workers.

Redmond et al., (1981) reported a statistically significant excess of mortality from chronic bronchitis and emphysema. However, mortality figures may not indicate the true extent of the problem. It is because the estimation has been made within the coke plant. There may be 3 to 4 times as much morbidity as mortality from these diseases.

Nilsen et al., (1984) also found a significantly increased number of macrophages in the expectorates of 43 exposed coke oven workers compared with 36 controls. Although the occupations of controls were not specified, the effect of smoking and exposure was again observed.

3.4 Summary

The acute and chronic health effects of these complex mixtures relate primarily to the skin, eyes and respiratory

system. A wide range of dermatological lesions have been described in the literature over a long period of time, culminating in the more comprehensive observational reports of Emmett (1977) and Gorman and Liss (1985). Ocular manifestations range from mild irritation to severe kerato-conjunctivitis. There is clearly an interactive effect with wavelengths of ultra-violet radiation as well as having implications in the carcinogenic potential of these compounds. The understanding of the mechanism of these phototoxic reactions primarily relate back to the stereo chemistry that was described in the previous chapter.

Acute respiratory irritation and chronic effects on the respiratory system such as chronic bronchitis, pneumonitis and emphysema have been observed in both animals and man.

Dose-response relationships of these types of observed health effects will be described in Chapter Seven for the purposes of risk assessment.

CHAPTER FOUR

ANIMAL CARCINOGENICITY AND MUTAGENICITY STUDIES

4.1 Animal Carcinogenicity

A large number of studies of animal carcinogenesis are reviewed in detail in this section as a background for a comparative analysis of the carcinogenicity of coal tar and petroleum products.

4.1.1 Animal Carcinogenesis - Coal Tar

Tsutsui (1918) applied coal tar to the skin of English mice. A total of 259 mice in seven groups were used; 67 mice survived for 100 days and 35 for periods ranging up to 166 days. Tumours were examined histologically and illustrated in photographs. Thirty-five (52%) of those who survived 100 days or more developed skin papillomas. Sixteen of these mice later developed skin carcinomas, two with lung metastases. One mouse had a spindle cell sarcoma. Fibiger and Bang (1920) and Bloch and Dreifus (1921) reported similar findings in subsequent studies.

Bonser and Manch (1932) applied three samples of Scottish blast furnace tar and one sample of English crude tar as well as an ether extract of the latter to the skin of sixty mice. The age, sex and strain were not specified. They received twice

weekly applications (dose not specified) of three different samples of the tars for 14 weeks followed by weekly applications for 56 weeks. By that time all the animals had died. "Warts" appeared after 16 weeks. Seven, ten, and eight animals in the respective groups developed skin tumours of which a total of three were found to be malignant. The first warts appeared in the 21st week in mice given the crude English tar and at the 12th week when an ether extract was used. Eight mice treated with the three Scottish tar samples and 24 mice treated with the crude English tar developed tumours. Nine tumours in mice given the ether extract were malignant. At 30 weeks there were 25 survivors in the latter group of mice and over 50% had tumours. The tumours were papillomas or squamous cell carcinomas of the skin. Carcinomas invaded the muscle. One malignant tumour, seen after 47 weeks of application of ether extract of English tar, consisted of a mass of "mononuclear round cells" invading the adjacent muscle and fat and metastasizing to the lymph nodes. In this study the blast furnace tar obtained from a variety of sources induced benign and malignant tumours in the skin of mice. The carcinogenic properties were enhanced by extraction with ether. If applied too frequently the tar caused ulcerations of the skin. It was noted that there was an absence of concurrent control groups.

Murray and Gaskell (1921) applied tar to the skin on the back of the neck of mice two or three times a week for several months. "Warty growths" appeared in some mice and the growths

increased in size as long as they were painted with tar. In contrast to the experiment done by Tsutsui, who had kept the mice painted with coal tar alive as long as possible in order to observe invasion and metastasis of tumour, the Murray study was carried out in order to find a more rapid method for determining if a tumour was malignant.

Dealman (1922) tested the action of horizontal retort tar and vertical retort tar in mice. Both tars produced papillomas. The change from benign to malignant occurred in the mice receiving horizontal retort tar.

In 1925, Kennaway described a series of studies on the formation of cancer-producing materials by the heating of oil and coal products. The products tested in the temperatures were: acetylene (700° C and 800° to 900° C), California petroleum (800° C), isoprene (700° C) and Durham Holmside coal (450°, 560°, and 1250° C). The tarry products were applied twice weekly to the intrascapular area of mice, generally 100 for each test. The first two tumours in mice given the 700° C product appeared on the 86th day. The first malignant tumour was on the 153rd day. Thirteen carcinomas with invasion and two papillomas were observed by the 258th day. There was a high mortality in mice receiving the 800° C to 900° C product; however, the author concluded that this tar was less effective at inducing tumours than was the 700° C product. The California petroleum used had been previously tested in the unheated state, and did not induce tumours. However, upon heating to 280° C in a current of

hydrogen the petroleum developed carcinogenic properties. The first benign tumour appeared on the 67th day after application to the mouse skin and the first malignant tumour was observed on the 170th day. The study was discontinued after 206 days when the ten surviving mice all had skin tumours.

When isoprene tar treated at 700° C was administered, tumours were observed in five mice after 87 days, three after 132 days and three after 168 days. The mice tested previously with 820° C tar developed more tumours of the skin. [The 700° C tar consisted chiefly of unsaturated and the 820° tar of saturated and aromatic compounds.]

When coal tar treated at various temperatures was administered, it was found that the tumour incidence was proportional to the temperature of the treatment. On the 230th day, 50% of the surviving mice given the 1250° C tar, 33% of the mice given the 560° C tar, and 4% of the mice receiving 450° C tar had skin tumours respectively. Most of the tumours were malignant in mice receiving the 560° C or 1250° C tar. This study demonstrated the importance of heat in the formation of cancer-producing substances in coal tar products. The carcinogenicity of coal tars and isoprene tar increased with an increase in temperature at which the tars were formed; however, with acetylene, low temperature products were more effective in producing tumours than the higher temperature.

Berenblum and Schoental (1947) undertook a study to determine whether carcinogens other than benzo a pyrene existed

in tar. They used horizontal retort tar of high carcinogenic potency. Tests for the carcinogenic action were carried out by skin painting once weekly in mice and twice weekly in rabbits. Since the object of the biological test was to determine in which of the fractions the carcinogens were present in high concentration, rather than to evaluate the exact potencies of the weaker fractions, relatively small groups of animals were used for each test and the studies only continued for sufficient time to be able to recognize which were the most active fractions. Consequently, failure to induce tumours did not necessarily denote complete absence of carcinogenic activity. In the study there were at least two potent carcinogens in tar apart from benzo[a]pyrene, one appearing chromatographically before and the other after benzo[a]pyrene.

Gorski (1959) tested benzene extracts (1:1) of two coal tars from different sources. Two groups of 30 mice (16 males and 14 females, strain not specified) were used. Each animal received a single drop of the test material applied with a dropper to the skin twice weekly for 22 weeks. After eight weeks of treatment there were 22 survivors in one group and 26 in the other. The recorded mean doses of tar applied after four months of treatment were 0.6 grams and 0.2 grams. After seven months, skin tumours were found in six of the 22 survivors in one group and eight of the 26 survivors in the other. No benzene control group was reported.

Hueper and Payne (1960) reported the effects of heated high

temperature coal tar obtained from a processor of coal carbon tars. These tars were applied twice weekly to the nape of the neck of 50 C57BL mice for up to two years. Twenty-five of each sex were used. Four of these animals developed papillomas and 22 developed carcinomas of the skin. There was an absence of concurrent controls and the survival data was not reported.

Shustova and Samoilovich (1971) studied the carcinogenic activity of a neutralized residual tar produced at a coke factory and used as a road surfacing material. This substance contained predominantly aromatics, naphthalene, anthracene, heterocyclics, and compounds containing oxygen such as phenol and cresols. Sulphur compounds such as thiophene and thionaphthene and nitrogen-containing substances such as pyridine, carbazole and pyrrole were also contained in this coal tar. The test substance contained benzo[a]pyrene at a concentration of 94 mg/kg. A group of 50 C57BL x $CBAF_1$ mice two to three months old were painted on the intrascapular skin with the neutralized tar diluted with benzene. The sex of the mice was not specified. One hundred grams of tar and 20 grams of benzene were used three times per week for ten months. After three months of treatment, three mice had skin tumours. After five months 50% had tumours. After six months 100% had tumours. Among 40 mice examined, histological analysis revealed 27 with squamous cell carcinomas five of which had metastases. Ten had papillomas and one had carcinoma. In a control group of 50 mice that received benzene only, no skin tumours were found.

A summary of the carcinogenic effects of coal tar in animal studies is shown in Table IV - 1.

4.1.2 Animal Carcinogenesis - Coal Tar Pitch

Barnewitz (1928) exposed an unspecified number of white mice kept in cages with a bedding consisting of coal tar pitch powder. The cages were shaken vigorously twice daily. Papillomas appeared after eight weeks and subsequently 59% of the mice developed skin carcinomas.

Murphy and Sturm (1925) conducted three experiments using a benzene extract of hard residue from coke oven tar. This tar had been collected at 377° C and washed with sodium hydroxide and sulphuric acid and then reconcentrated from benzene. A total of 40 mice of unspecified sex and stock had this extract applied on 12 different areas of each mouse. The application sites were rotated so that each area received only three applications about one month apart over an 83 day period. Of 23 mice aged nine to ten months killed four months after the last administration, 21 had lung tumours. Of the 12 mice killed at one to six months, and of another group of five surviving mice receiving the same treatment and killed at six months after the last administration, 13 had lung tumours which were confirmed by histological examination. In two control groups, one of 22 mice aged eight to 12 months, and one of 16 mice aged 12 to 16 months, no lung tumours were reported. No skin tumour was found in treated or

Table IV - 1 Summary of the Carcinogenic Effects of Coal Tar in Animal Studies

Author/year	Exposed to	Concentration and Duration	Species	No. of Animals	Effects/Outcomes
Tsutsui 1918	Bituminous Coal	Applied to skin	Mice (English)	259	Papillomas, carcinomas and spindle cell sarcoma
Bonser and Manch 1932	Scottish Blast Furnace Tar; English Crude Tar	Applied bi-weekly to skin for the first 14 weeks, and thereafter, once weekly for 56 weeks	Mice	60	Papillomas and squamous cell carcinomas of the skin
Murray 1921	Coal Tar	Applied tar to the skin, two or three times a week for several months	Mice		Warty growths in skin
Kennaway 1925	Coal Tar	Coal tar products of 450 deg C, 560 deg C and 1250 deg C distillation temperature applied twice weekly to mice, in the intra-scapular area	Mice	100 per test	Skin tumours (the higher the temperature the higher the rate of carcinogenesis)
Berenblum and Schoental 1947	Coal Tar Chromato-graphic fractions	Applied to skin, 16 weeks duration	Mice Rabbits	100 25	30 developed skin tumours
Gorski 1959	Hard Coal Tar	Applied to skin, 1:1 in benzene, bi-weekly for 22 weeks	Mice	21	8 developed skin tumours
Gorski 1959	Soft Coal Tar	Applied to skin, 1:1 in benzene, bi-weekly for 22 weeks	Mice	28	14 developed skin tumours
Hueper and Payne 1960	Coal Tar Fume Condensate	By injection, thigh intramuscular, 1:3 in olive oil, 0.15 ml bi-weekly with 6 doses	Mice	100	50 developed sarcomas

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Table IV - 1
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Hueper and Payne 1960	Coal Tar Fume Condensate	Applied to skin, 1:3 in olive oil	Mice	50	22 carcinomas and 4 papillomas occurred
Hueper and Payne 1960	Coal Tar	By inhalation, Vaporized 250 - 275 deg F 5 hrs/day 4 days/week 2 years	Guinea Pigs Rats	42 75	No cancer of skin or lungs
Shustova and Samoilovich 1971	Neutralized Residual Tar	Applied to skin, 100 gm of tar and 20 gm of benzene, 3x/week for 10 months	C57BLX, CBAF, mice of 2-1/2 to 3 months	50	After 3 months, 3 mice had skin tumours. After 5 months, 50% had tumours. After 6 months, 100% had tumours.

control mice.

Gorski (1959) exposed groups of 30 mice (16 males and 14 females of unspecified strain) to benzene extracts of hard pitch, soft pitch or anthracene fraction all from a single source. Each animal received a single drop of the test material applied with a dropper on the skin twice weekly for 22 weeks. After eight weeks of treatment the survivors numbered 21, 28 and 24 in the hard pitch, soft pitch and anthracene groups respectively. The reported mean doses of corresponding products applied after four months of treatment were 1.0 (hard pitch), 2.9 (soft pitch) and 0.3 (anthracene) grams per mouse. Skin tumours were found in eight of the 21 survivors in the hard pitch group, 14 of the 28 survivors in the soft pitch group and four of the 24 survivors in the anthracene group at the end of the seven month experimental period. No benzene control group was reported.

Kireeva (1968) reported on the results of a group of 49 CC-57 white mice treated by weekly skin applications of 40% coal tar pitch in benzene over 19 months. The first skin tumour appeared three months after the start of the experiment, at which time 43 mice were still alive. By the end of 12 months skin tumours had occurred in 37 of these survivors. The majority of these tumours were squamous cell carcinomas.

Wallcave et al., (1971) reported on the carcinogenic activity of two samples of coal tar pitches from coke oven production tested on the skin of Swiss albino mice. Coal tar pitches were applied as solutions in benzene with a tar content

less than 9%. Applications were made twice weekly with a dropper calibrated to deliver 25 microlitres of solution. This corresponded to approximately 1.7 mg of coal tar pitch per application. The mean survival time for treated animals was 31 weeks whereas the control animals survived 82 weeks. The two coal tar pitches induced skin tumours in 27 of 29 mice and in 26 of 29 mice which survived with 13 and 18 carcinomas and 27 and 26 papillomas respectively. One of the 26 benzene-treated mice developed one papilloma.

Emmett et al., (1981) studied the carcinogenic activity of:

1) traditional roofing coal tar pitch;
2) two coal tars with oftening points of 65° C and 68.3° C respectively;
3) coal tar from roofing operations; and
4) roofing dust representative of particulate matter from the site of removal of a 25 year old roof containing coal tar pitch.

All samples were dissolved in toluene in a 1 to 1 ratio, weight to weight, and were applied with either a microlitre pipette or a calibrated glass dropper to the intrascapular shaved skin of male C3H/HeJ mice. Each exposed group consisted of 50 mice except the group treated with the roofing dust, the latter group consisting of 20 mice. Mice were treated twice weekly for 80 weeks with 50 mg of the resulting solution. A negative control group received 50 mg of toluene twice weekly. A positive control group received

50 mg of benzo[a]pyrene under the same conditions in a 0.1% toluene solution. The number of tumour-bearing animals were 48 out of 49 for exposure (1); 47 of 48 for exposure (2); 42 of 45 or exposure (3); and 12 of 14 for exposure (4). The majority of these skin tumours were malignant, groups having 45, 43, 38 and 10 tumours respectively. In toluene-treated mice no tumours were observed whereas in the benzo[a]pyrene positive control group 31 of 39 mice developed tumours of which 24 were malignant. In the groups receiving samples containing coal tar pitch, the average latency period ranged from 16.5 to 21.5 weeks, whereas for the group receiving benzo[a]pyrene the average latency period was 31.8 weeks.

A sample of coal tar pitch emissions collected from a conventional tar pot with an external propane burner with a temperature of 182° to 193° C (dichloromethane extract) was studied by skin application for initiating activity, complete carcinogenic activity, and promoting activity. The material under consideration was described by Lewtas (1981); Nesnow (1982); Albert (1983); and Austin et al., (1984). To evaluate the initiating activity, five groups of 40 male and 40 female SENCAR mice, seven to nine weeks of age, were treated with roofing tar extract dissolved in 0.2 ml of acetone. Topical applications of 0.1, 0.5, 1.0, 2.0 or 10 mg were given. The 10 mg dose was administered as five daily doses of 2 mg. Beginning one week after treatment doses of 2.0 micrograms of 2-tetradecanoyl-phorbol-13-acetate (TPA) and 0.2 ml of acetone were applied

topically twice weekly. Another group of mice was treated with TPA only. After six months of the treatment the percentages of mice with papillomas were 12.5, 20.5, 41.5, 36.5, 97 in the treated groups, respectively, and six for the controls. One year later the percentages of the mice with carcinomas were 7.5, 14, 10, 14 and 35.5 for the tar initiated groups and 2.5 for the TPA controls. These studies were reported in a series of publications by Lewtas et al (1981); Nesnow and Lewtas (1981); Slaga et al (1981); and Nesnow (1982, 1983). To evaluate the complete carcinogenic activity five groups of 40 male and 40 female SENCAR mice were treated topically with the same roofing extract dissolved in acetone. Weekly applications of 0.1, 0.5, 1.0, 2.0 and 4.0 mg per mouse were given in a 0.2 ml of acetone for 50 to 52 weeks. The 4 mg doses administered as two doses of 2 mg. The cumulative percentages of mice with carcinomas after one year were 0, 1.0, 1.5, 5.5, and 26.5 respectively. This study was reported by Nesnow et al., (1983). For the promoting activity six groups of 40 male and 40 female SENCAR mice were treated topically with single doses of 50.5 micrograms benzo[a]-pyrene in 0.2 ml of acetone. One week later five of the six groups were treated with roofing tar extract dissolved in 0.2 ml of acetone. Weekly applications divided into two doses for the highest dose of 0.1, 0.5, 1.0, 2.0 and 4.0 mg per mouse were given for 34 weeks. The sixth group was treated with 0.2 ml of acetone. The percentages of mice with papillomas at 34 weeks were 0, 2.5, (male 5; female 0), 18 (male 20; female 16), 18

(male 3; female 13) and 42.5 (male 55; female 30), respectively. No mouse with a tumour was reported in benzo[a]pyrene initiated and acetone treated groups. This study was reported by Nesnow et al., (1983).

A summary of the carcinogenic effects of coal tar pitch in animal studies is shown in Table IV - 2.

4.1.3 Animal Carcinogenesis - Creosote

Cabot et al., (1940) exposed groups of 20 female albino random bred mice to a basic fraction of creosote. They were painted with benzene solutions containing 0.2% or 0.05% benzo[a]-pyrene or 0.2% or 0.05% benzo[a]pyrene together with a creosote oil, 90% of which were distilled at 160° to 300° C or various fractions thereof. The test materials were applied to the shaven back by five strokes of a swab dipped once into the test solution. The benzene solution containing 0.2% benzo[a]pyrene was applied three times weekly for 20 weeks and twice weekly for six weeks totalling 72 applications in 26 weeks. The solution containing 0.05% benzo[a]pyrene was applied three times weekly for 38 weeks or 114 applications. Animals developing papillomas 4 mm in diameter which did not regress were classified as tumourbearing. Time to first appearance of tumours was recorded. Tumours developed in 19 of 20 animals receiving 0.2% benzo[a]-pyrene and benzene, in 12 of these after 13 weeks. Tumours were induced after 22 weeks in 16 of 20 animals receiving 0.05%

Table IV - 2 Summary of the Carcinogenic Effects of Coal Tar Pitch in Animal Studies

Author/year	Exposed to	Exposure Route, Concentration and Duration	Species	No. of Animals	Effects/Outcomes
Murphy and Sturm 1925	Benzene extract of hard residue from coal tar distilled at 377 deg C and washed with sodium hydroxide and then sulphuric acid	Applied to 12 different areas of the skin, 3x/ week for 3 months	Mice (fairly uniform stock)	70	34 had lung tumours
Barnewitz 1928	Coal tar pitch	Mice kept in cages with a bedding of coal tar pitch powder, cages shaken vigorously twice daily	White mice		Papillomas appeared after 8 weeks and subsequently 59% of the mice developed skin carcinomas
Gorski 1959	Coal tar pitch from Silesian Coals	Applied to skin, 1:1 in benzene bi-weekly for 22 weeks	Mice	48	14 developed skin tumours
Kireeva 1968	Coal tar pitch	Applied to skin, 40% in benzene once per week for 19 months	Mice (SS-57 white)	49	29 carcinomas + 8 papillomas (at 12 months)
Wallcave et al. 1971	Coal tar pitch roofing	Applied to skin, 9% benzene (filtered) 25 ul bi-weekly	Mice (Swiss)	58	31 carcinomas and 53 papillomas
Emmett et al. 1981	Coal tar pitch	50 mg (50% toluene) to the intra-scapular shaved skin of mice, bi-weekly for 32 weeks	Male mice (C3H/HeJ)	50	45 with malignant tumours 3 with benign tumours
Emmett et al. 1981	Roofing dust (containing coal tar pitch)	50 mg (50% toluene) to the intra-scapular shaved skin of mice, bi-weekly for 48 weeks	Male mice (C3H/HeJ)	50	10 with malignant tumours 2 with benign tumours

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Table IV - 2
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Nesnow et al. 1982	Roofing tar	Applied to skin as a single topical treatment in 0.2 ml of acetone except for the 10 mg dose, which was administered in 5 daily doses of 2 mg. Beginning one week after treatment doses of 2.0 ug of 2-tetradecanoyl-phorbol-13-acetate (TPA) and 0.2 ml of acetone were applied topically twice weekly for 34 weeks	Mice (Sencar)	40 m 40 f	Tumour multiplicity ranged from 5 to 6 papillomas

benzo[a]pyrene in benzene. A 1% solution of creosote obtained by aqueous hydrochloric acid extraction increased benzo[a]pyrene tumorigenesis with respect to both time to appearance of tumours and number of tumours. A phenolic fraction obtained by extraction into aqueous sodium hydroxide exhibited an enhancing effect. This effect was more marked with the lower concentration of benzo[a]pyrene. Phenolic and basic fractions tested alone failed to induce tumours.

Sall and Shear (1940) examined the modifying effects of benzo[a]pyrene-induced tumorigenesis. A group of 100 female strain A mice was divided into 5 sub-groups and painted three times a week with a 1% solution of the basic fraction in benzene, 0.02% or 0.05% benzo-[a]pyrene and benzene, or 0.05% benzo[a]-pyrene in benzene containing 1% of the basic fraction of creosote. No tumour was produced in any of the mice receiving a basic creosote fraction alone. However, the latent period for tumour appearance was shorter in the group which was receiving benzo[a]pyrene in the basic fraction of creosote as compared to that from mice receiving benzo[a]pyrene alone, suggesting that the basic fraction of creosote decreases the latency effect of the tumorigenicity to benzo[a]pyrene.

Woodhouse (1950) reported that full-strength creosote oil and anthracene oil was tested in groups of 50 male and female albino white mice by twice weekly applications for at least 25 weeks. In the group that received creosote oil, ten of the 19 animals surviving were found to have papillomas and nine had

large keratinizing carcinomas. In the group receiving anthracene oil, eight of the 20 mice surviving at 25 weeks were thought to have papillomas and six had large keratinizing carcinomas. No concurrent control group was used. Pine oil and linseed oil-exposed mice did not have any skin tumours under similar experimental conditions.

Poel and Kammer (1957) exposed the skin of groups of 10 female C57Bl mice for the lifespan of the animal or until skin tumours developed with 1 drop of a 20% or 80% solution of creosote. All mice exposed to dilutions developed papillomas and seven of the eight affected mice in each of the two groups developed epidermoid carcinomas, some of which metastasized to the pulmonary or regional lymph nodes. The time to papilloma appearance in 50% of the animals was 26 and 21 weeks in those receiving 20% and 80% solutions of creosote respectively. Control animals receiving toluene did not develop any skin neoplasms. A light creosote oil derived from residual oil of the naphthalene recovery operation was tested in male C57Bl mice by applying one drop of a 50% solution in toluene three times a week for life. Of 11 mice surviving 20 or more weeks of treatment, all developed skin tumours within 45 weeks. Lijinsky et al., (1957) exposed a group of 30 female Swiss mice to undiluted creosote oil which was applied twice weekly for up to 70 weeks. The effective number of mice surviving at the appearance of first tumour was 26. Of these, 13 were found to have 23 skin tumours of which 16 were considered carcinomas. The average latent

period for development of tumours was 50 weeks. No control group was used in these experiments.

Saffiotti and Shubik (1956) reported that the carcinogenic effect of creosote was considered almost identical in potency to that of repeated applications of a 0.01% solution of 7,12-dimethylbenz[a]anthracene in mineral oil. Lijinsky et al., (1957) applied a 2% solution of the basic fraction of creosote oil and acetone twice weekly for 70 weeks to a group of 30 mice following a single painting with one drop of a 1% solution of 7,12-dimethylbenz[a]anthracene in mineral oil. At 56 weeks, 12 mice survived. None of these had skin tumours or developed them up to 70 weeks. The basic fraction alone was not tested.

Boutwell and Bosch (1958) applied undiluted creosote twice weekly in amounts of 25 microlitres to the skin of 30 random bred female mice. At the end of 28 weeks, the mice had an average of 5.4 papillomas and 82% had carcinomas. In a similar application of creosote to another group of 30 mice for only four weeks followed by 32 weeks of observation, resulted in no skin tumours. A third group treated with creosote for four weeks followed by twice weekly applications of 25 microlitres of 0.5% croton oil in benzene developed 2.8 papillomas per mouse at 28 weeks and 4.4 papillomas per mouse at 36 weeks. At week 44, 46% had carcinomas. A control group given croton oil only, also developed skin tumours in lower incidences, but by four weeks eight of the 26 mice given croton oil had 13 papillomas and one carcinoma compared to 0.1 papilloma per mouse at 28 weeks.

Roe et al., (1958) using the same creosote as the above experiment on a group of 24 albino mice treated topically with 25 microlitres of creosote twice weekly for six months, showed after two additional months of observation 139 lung adenomas or 5.8 tumours per mouse. Nine lung adenomas were observed in 19 control mice with 0.5 tumours per mouse. In addition, a group of 29 mice born and kept in creosote impregnated wood cages received skin painting with 25 microlitres of creosote twice weekly for five months starting after weaning. At eight months of age they showed 315 lung adenomas or 10.8 per mouse. In the second experiment a different lot of albino mice aged two months were treated by skin application of 25 microlitres of the same creosote twice weekly for four weeks or nine applications. After ten months 37 lung adenomas in 23 mice were observed or 1.6 tumours per mouse. In 50 similar mice with croton oil or benzene 15 lung adenomas were found or 0.3 tumours per mouse.

A summary of the carcinogenic effects of creosote in animal studies is tabulated in Table IV-3.

Table IV -3 Summary of the Carcinogenic Effects of Creosote in Animal Studies

Author/year	Exposed to	Exposure Route, Concentration and Duration	Species	No. of Animals	Effects/Outcomes
Cabot et al. 1940	Creosote oil	Painted with 3,4-benzpyrene with 0.2 or 0.05% distilled at 160 to 300 deg C 3x/weekly for 20 weeks and bi-weekly for 6 weeks	Albino Mice	20	The 0.05% benzpyrene control solution began to produce skin tumours after most of the mice painted with 0.2% benzpyrene control solution already bore tumours
Sall and Shear 1940	Creosote oil	Painted with 3,4-benzpyrene with 0.2 or 0.05% and benzene containing 1% of the basic fraction of creosote	Female Mice	100	Tumours were obtained, but no tumour developed in mice receiving a basic creosote fraction alone
Woodhouse 1950	Creosote oil	Bi-weekly applications to skin about 1-1/2 cm in diameter was covered for 25 weeks	Albino Mice	25 m 25 f	Creosote oil gp-10 had papillomas and 9 had keratinizing carcinomas. Anthracene oil gp-8 had papillomas and 6 had keratinizing carcinomas
Poel and Kammer 1957	Creosote oil	Treated topically with a 20 or 80% dilution of light creosote 3x/week for life, or until skin tumours developed	Female Mice	10	All mice developed papillomas, and 7 of the 8 affected mice in each of the 2 gp developed epidermoid carcinomas and metastases were evident
Lijinsky et al. 1957	Creosote	Treated topically bi-weekly for 70 weeks, with undiluted creosote, a 10% or a 2% solution of the basic fraction	Mice (Female Swiss)	30	23 skin tumours of which 16 were considered carcinomas
Boutwell and Bosch 1958	Creosote	Undiluted 25 ul creosote bi-weekly to the skin for 28 weeks	Random Bred Female Mice	30	An average of 5.4 papillomas and 82% had carcinomas
Boutwell and Bosch 1958	Creosote	Undiluted 25 ul creosote bi-weekly to the skin for 4 weeks	Random Bred Female Mice	30	No skin tumours

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Table IV - 3
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Boutwell and Bosch 1958	Creosote	Creosote for 4 weeks followed by twice weekly applications of 25 ul of 0.5% croton oil in benzene	Random Bred Female Mice	30	2.8 papillomas per mouse at 28 weeks and 4.4 papillomas per mouse at 36 weeks. At week 44, 46% had carcinomas
Roe et al. 1958	Creosote	Treated topically with 25 ul of creosote bi-weekly for 6 months	Albino Mice	24	139 lung adenomas or 5.8 tumours per mouse

4.1.4 Animal Carcinogenesis - Coke Oven Emissions

The carcinogenicity of topside and main oven emissions was tested as a tumor initiator in SENCAR mice (Nesnow et al., 1982, 1983). Topside coke oven samples were extracted with dichloromethane, which was subsequently removed by evaporation under dry nitrogen gas. The extract was found to contain benzo[a]pyrene at a level of 478 mg/kg. Groups of 40 male and 40 female mice per treatment group were painted once only with 0.1, 0.5, 1.0, 2.0 or 10 mg of each sample (Topside coke-oven and coke-oven main) dissolved in 0.2 ml acetone. The 10 mg dose was administered in divided doses of 2.0 mg each for 5 days. After one week, 2 ug of 12-0-tetradecanoylphorbol-13 acetate (TPA) were applied topically twice weekly. Control groups were treated with TPA only or with a single dose of benzo[a]pyrene followed by TPA were included. The incidences of papillomas and of carcinomas were reported at six months and one year respectively. Results are shown in Table IV-4.

In the report of the following year (Nesnow et al., 1983), the coke-oven main sample was applied topically to groups of 40 male and 40 female mice at 0.1, 0.5, 1.0, and 2.0 mg per mouse on a weekly basis, the highest dose (4.0 mg) was applied bi-weekly at 2.0 mg per application for 50-52 weeks. Control groups were treated with acetone or benzo[a]pyrene once weekly for a period of 50-52 weeks. Results are shown in Table IV - 5.

Table IV - 4. Skin tumours observed following administration of a single dose of benzo[a]pyrene (B[a]P), topside coke-oven extract, and coke-oven main extract to SENCAR mice followed by repeated administrations of 12-O-tetradecanoylphorbol-13-acetate (TAP) twice weekly.*

Sample	Dose mg/mouse	Sex	Mice with papillomas %	Mean No. of papillomas per mouse+	Mice with carcinomas++ %
TPA alone	0	M	8	0.08	5
	0	F	5	0.05	0
B[a]P	0.1	M	95	10.2	30
	0.1	F	97	7.9	25
Topside coke oven	0.1	M	13	0.13	0
	0.1	F	10	0.20	8
	0.5	M	73	1.6	5
	0.5	F	70	1.8	15
	1	M	95	2.6	15
	1	F	72	2.0	3
	2	M	95	4.0	13
	2	F	90	3.5	10
	10	M	100	7.1	13
	10	F	100	7.7	20
Coke-oven main	0.1	M	50	0.63	10
	0.1	F	31	0.38	25
	0.5	M	90	3.7	54
	0.5	F	92	2.2	54
	1	M	87	3.3	53
	1	F	90	3.1	48
	2	M	78	3.1	48
	2	F	100	5.3	45
	10	M	100	8.9	55
	10	F	100	8.1	65

* From Nesnow et al. (1982, 1983)
+ Scored six months after initiation
++ Cumulative score one year after initiation

Table IV - 5. Skin carcinomas following repeated administration of SENCAR mice of samples of coke-oven main for 50-52 weeks.

Sample	Dose (mg/mouse per wk)	Sex	Carcinomas (% incidence)
Acetone	-	M	0
	-	F	0
Benzo[a]pyrene	0.0051	M	93
	0.0051	F	98
Coke-oven main	0.1	M	5
	0.1	F	5
	0.5	M	36
	0.5	F	30
	1	M	48
	1	F	60
	2	M	82
	2	F	78
	4	M	98
	4	F	75

From Nesnow et al, (1983)

Results of both the topside and main samples, which produced dose-related increases in both papillomas and carcinomas (Nesnow et al., 1982, 1983), are shown in Table IV - 5. With reference to the topside sample, the papilloma incidence ranged from 10-100% and carcinomas ranged from 0.20%, whereas with the coke-oven main sample, papilloma incidence ranged from 31-100% and carcinomas from 10-67%.

Horton et al., (1963), in an inhalation exposure study, investigated C3H mice for lung tumors following inhalation exposure to coal tar aerosol, gaseous formaldehyde, or gaseous formaldehyde followed by coal tar aerosol. Four groups of mice were examined. The first was the control group consisting of 59 untreated mice. A second group of 33 mice was exposed to a coal-tar aerosol administered at a rate of 300 mg/m^3 for three 2-hour periods per week up to 36 weeks. Two squamous-cell tumors of the lung, one of which was malignant as well as a pulmonary adenoma developed in this group. In addition, squamous cell metaplasia of the bronchial epithelium were observed. Three squamous-cell tumors of the lung also developed. A third group of 60 mice was exposed to formaldehyde vapour at 100 mg/m^3 for three 1-hour periods each week for up to 35 weeks, at which time 26 mice were still alive. They were then exposed to the coal-tar aerosol at a concentration of 300mg/m^3 for three 2-hour periods per week. One squamous-cell tumour and one pulmonary adenoma were seen in the lung of a mouse that died between weeks 47-58. By week 68, all mice had died. No lung

tumor occurred in mice exposed to formaldehyde at 50 mg/m^3 for 35 weeks and then at 150 mg/m^3 for up to 68 weeks. In summary, mice inhaling coal tar aerosol developed squamous cell carcinomas of the lung, as well as hyperplastic and metaplastic epithelial changes involving primarily the trachea.

In another study by Tye and Stemmer (1967), two different coal tars, Tar 1 (specific gravity 1.17; 4.5% tar acid, 0.7% benzo[a]pyrene, and 67% Diels-Adler compounds), and Tar 2 (specific gravity 1.24; 1.4% tar acid, 1.1% benzo[a]pyrene and .2% Diels-Adler compounds), both derived as by-products from coke ovens, were separated into phenolic (P-tar) and non-phenolic (N-tar) phases. Six groups of 50 male C3H/HeJ mice, 3 to 5 months old were treated with air only or with aerosols of Tar 1, N-Tar 1, N-Tar 1 plus P-Tar 1 re-added, N-Tar 1 plus P-Tar 2, or N-Tar 2 plus P-Tar 1. The animals were exposed for two hours every three weeks. During the first eight weeks, the exposure was at a concentration of 0.20 mg/liter, but this was reduced to 0.12 mg/liter because many mice died. The experiment was terminated at the end of 55 weeks. There were 62%, 22%, 20%, 42% and 42% of the mice alive in the control, Tar-1, N-Tar-1, N-Tar-1 plus P-Tar-1, N-Tar-1 plus P-Tar-2, and N-Tar-2 plus P-Tar-1 groups, respectively. No lung tumor was observed in the animals exposed to air only. Tumor response of the treated mice is summarized in Table IV-6.

Table IV - 6. Incidence of Lung Tumors in Mice+ Inhaling Aerosols of Coal Tars* Derived as By-products from Coke Ovens

Treatment	Metaplasia	Adenomast	Adenocarcinomas	Adenomas and Carcinomas
Untreated Controls	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/32 (0%)
Tar-1	5/13 (38%)	12/13 (92%)	3/13 (23%)	13/13 (100%)
N-Tar-1	2/20 (10%)	16/20 (80%)	0/20 (0%)	16/20 (80%)
N-Tar-1# P-Tar-1	5/19 (26%)	14/19 (74%)	1/19 (5%)	15/19 (79%)
N-Tar-1# P-Tar-2	7/25 (28%)	14/25 (56%)	1/25 (4%)	15/25 (60%)
N-Tar-2# P-Tar-1	4/23 (17%)	14/23 (61%)	0/23 (0%)	14/23 (61%)

* From Tye and Stenner 1967

+ Mice surviving for 46 weeks or longer.

Includes intrabronchial and alveolar adenomas.

MacEwen et al., (1976) examined a group of 75 female ICR-CF mice (described as tumor susceptible), and a group of 50 female JAX-CAFI mice (described as a tumor-resistant hybrid strain), and 40 male and 40 female CFN strain Sprague-Dawley weanling rats. The treated groups were exposed to the coal-tar aerosol (a composite mixture collected from the effluents of several different coke ovens in the area of Pittsburgh, PA, USA) at a concentration of 10 mg/m^3 for six hours per day, five days per week for a total of 18 months. An equal number of male and female controls was available. Skin tumors were produced in 5/61 treated ICR-CF mice and 2/50 treated CAF-JAX mice as compared to 3/68 and 1/48 of the respective controls. The exposed and control groups did not differ in the incidence of other types of tumors. The authors suggested that the 18-month intermittent exposure of the animals in their study allowed enough time each day for the animal to do their normal fur cleaning. The incidence of tumors in the rat group is reported in Table IV-7. The incidence of squamous cell carcinomas in the lung was 100% in exposed males and 82% in exposed females as compared to 0% in male controls and 0% in female controls.

Table IV - 7. Coke Oven By-product Coal Tar Tumorigenesis in Rats*

	Controls		Exposed	
	Males	Females	Males	Females
Number Examined Histololgically#	30	37	38	38
Number of Rats with Tumors:				
Squamous Cell Carcinoma, Lung	0	0	38	31
Squamous Cell Carcinoma	0	1	0	0
Intra-abdominal Carcinoma	0	1	0	0
Mammary Fibroadenoma	0	1	0	3
Other Tumors	0	1	8	2
Overall Tumor Incidence (%)	0	13	100	82

* From MacEwen et al. 1976

The original number of rats per group was 40. However, because of autolysis and/or cannibalization, a few animals were unsuited for histopathological examinations.

4.1.5 Animal Carcinogenesis - Asphalt

Hueper and Payne (1960) did skin painting experiments on a group of 50 C57 black mice. Twenty-five male and 25 female mice were painted twice weekly on the nape of the neck with the heated sample of an air-blown asphalt used for roofing purposes. The dose was not specified. Treatment was continued for up to two years. One skin carcinoma was reported. No control group was used. The data on survival of the group was not reported. In another experiment one group of 100 and three groups of 50 male and female black C57 mice were treated by skin application with road petroleum asphalt obtained by steam distillation of crudes from Venezuela, Mississippi and California and by steam vacuum distillation of one Oklahoma crude respectively. Each mouse received one drop of asphalt liquefied with acetone on the neck skin twice weekly for up to two years. One skin carcinoma was observed in a group treated with Mississippi sample and one skin papilloma was observed in the groups treated with Oklahoma and Mississippi samples. No skin tumour was found in the groups treated with the Venezuela or California samples or in 100 untreated mice.

Simmers et al., (1959) used a pooled sample of six steam and airblown oxidized petroleum asphalts liquefied with benzene. They applied this twice weekly onto the intrascapular skin of 68 C57 black mice. Thirty-two males and 36 females were in this group. Sixty-three mice (31 males and 32 females) were similarly

treated with benzene alone. Epidermoid carcinomas appeared on the skin of 12 treated animals, the first tumour appearing during the 54th week after the beginning of the experiment. No tumour was found in control animals.

Simmers (1965) heated steam refined petroleum asphalt and applied this to the skin of 50 C57 black mice three times weekly. Originally he started with 25 males and 25 females but only 14 males and 18 females survived an epidemic of pneumonitis. This occurred seven weeks into the experiment and only one male and five females were alive after one year. Eight males and five females were added to the group. The number of paintings ranged from 16 to 240. Topical squamous cell carcinomas were found in three of 21 autopsied mice. A further group of 50 mice were treated one to three times weekly with treated air-refined oxidized petroleum. No carcinoma was observed at the site of treatment in 32 mice surviving more than seven weeks. Ten were autopsied of this group.

In a complementary group of 10 males and 10 females, the air-refined oxidized petroleum diluted in toluene was applied three times weekly for up to two years with a total of 284 applications. Topical squamous cell carcinomas developed in nine of the 20 mice autopsied. Of 15 toluene-treated control animals, one developed skin papillomas. The data on subsequent survival of this group was incomplete. In another experiment in the same year, Simmers used a mixture of aromatics and saturates isolated by fractionation of steam refined asphalt from a California crude

petroleum. This was applied three times weekly with about 33.4 mg per application to the intrascapular non-shaved skin of 25 male and 25 female C57 black mice. The number of applications ranged from 72 to 242 because of differential survival. Of 30 mice studied microscopically, 13 showed skin papillomas and cancers. Seven of these were epidermal-like carcinomas and five were basal squamous cancers.

Niemeier et al., (1985) investigated the relative tumorigenicity to mouse skin of condensed volatile components of roofing petroleum asphalts and coal tar pitches. A primary factorial experiment involving 32 groups of 50 mice each was carried out. The experimental variables consisted of two strains of mice, (CD-1 and C3H/HeJ); four initial roofing materials (asphalt, Types I and III; coal tar pitch, Types I and III); two temperatures of generation of volatile fume materials 232° and 316° C; and the exposure to simulated sunlight versus the absence of such exposure. The exposure to the condensed volatiles and light was done for a period of 18 months twice weekly. Other test variables consisted of alternate weekly applications of volatiles derived from Type III petroleum asphalt and Type I coal tar at 316° C compared to positive controls with benzo[a]pyrene, with and without sunlight exposure; and negative controls with exposure to solvent and sunlight. Skin tumor incidence is shown in Figure IV - 1, and the mean latency time is shown in Figure IV - 2. It was found from these studies that the temperature used in the preparation of the condensed fume

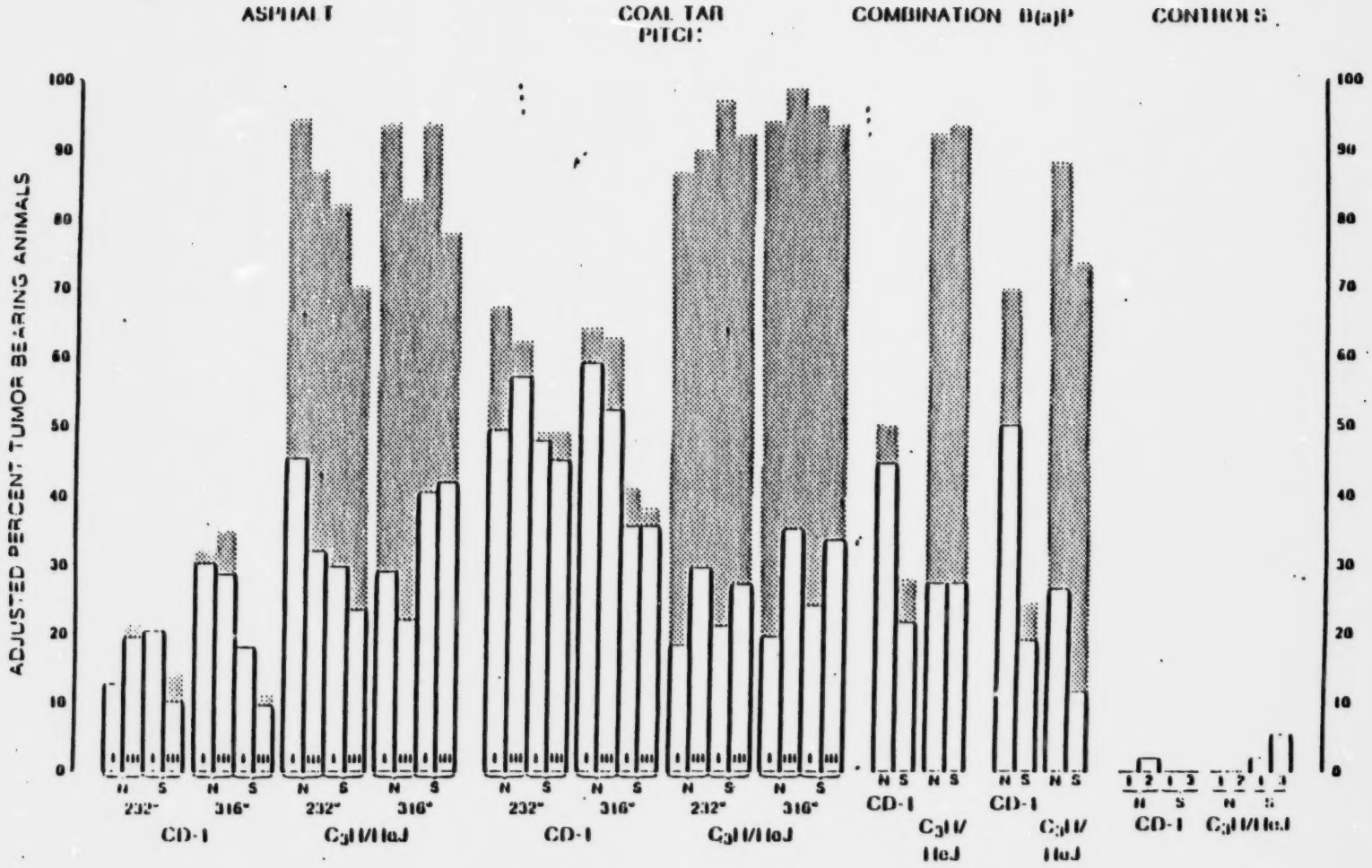


FIGURE IV--1 --SKIN TUMOR INCIDENCE. Corrected for number at risk at the appearance of the first tumor. Open and hatched bars represent benign and malignant tumor proportions, respectively. Controls: 1 = solvent group + light, 2 = cage control, and 3 = light exposed only. Types of materials are designated by I or III as noted in the text. N denotes no simulated sunlight exposure; S indicates a solar exposed group.

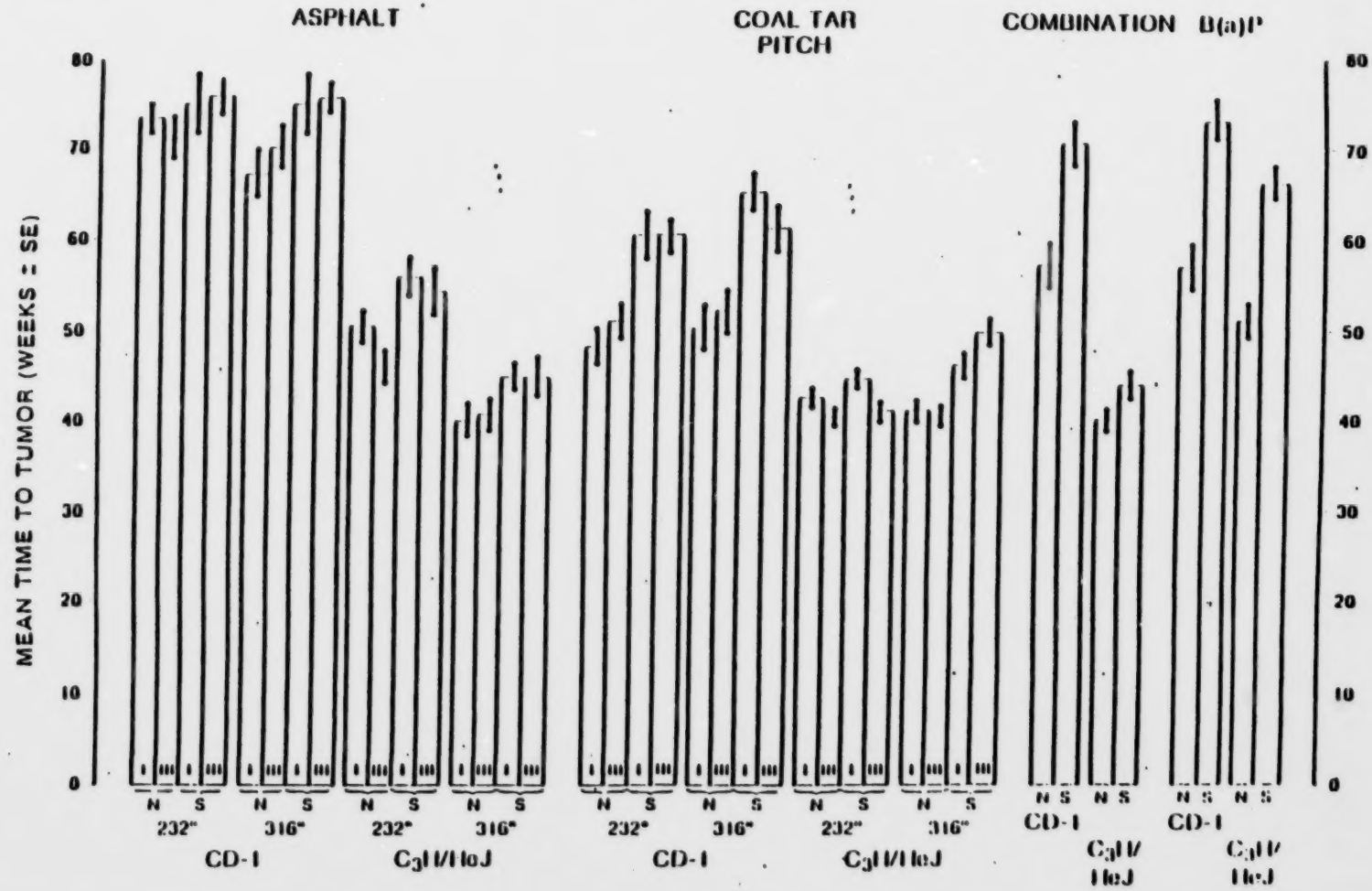


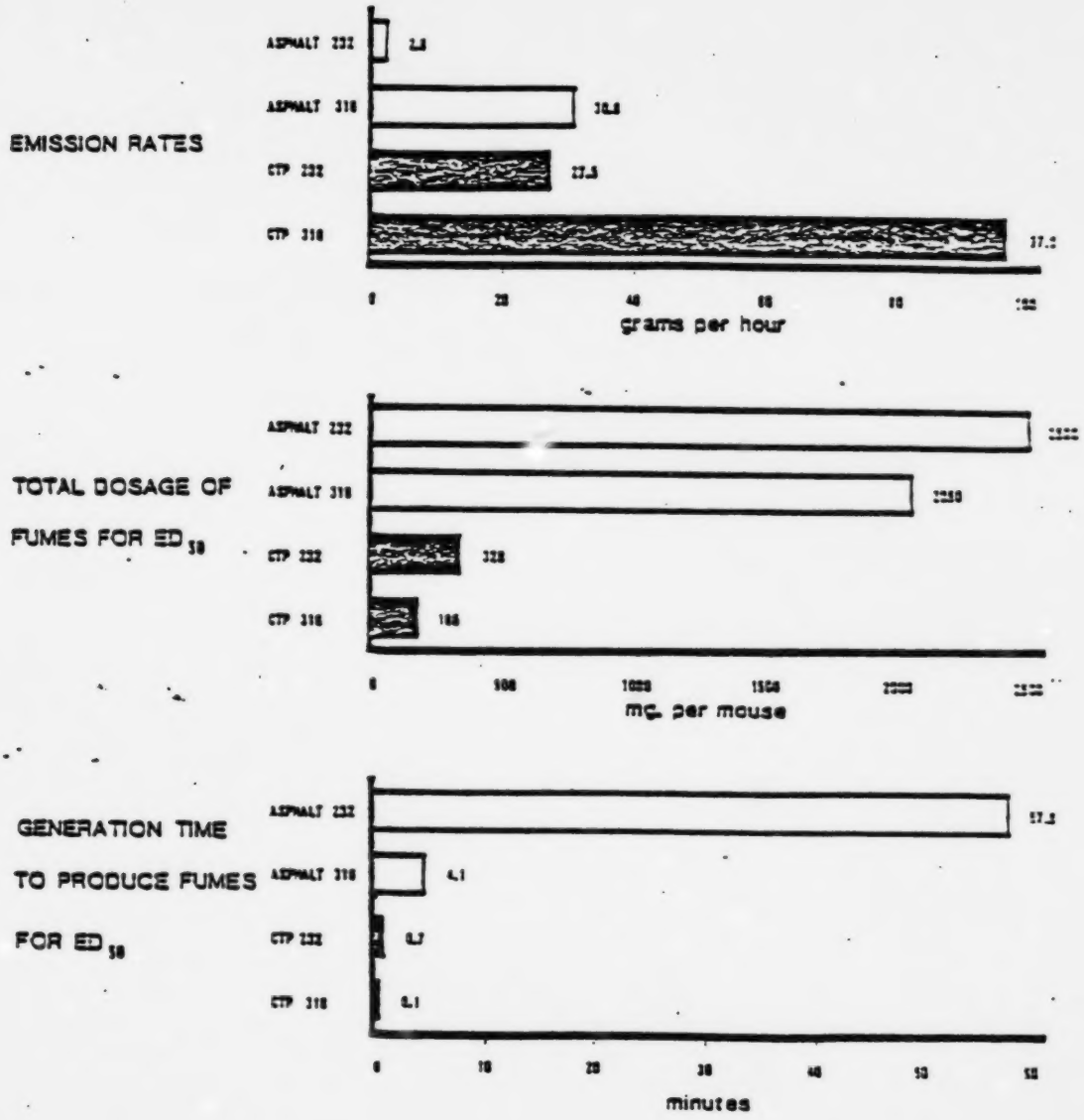
FIGURE IV-2 --MEAN LATENCY TIME. Expressed in weeks ± standard error based on histopathologically confirmed tumors. Types of materials are designated as I or III. N denotes no simulated sunlight exposure; S indicates a solar exposed group.

material had a pronounced effect on tumorigenesis. A comparison of generation times necessary to produce sufficient roofing material fumes for an ED_{50} tumorigenic response in mice is shown in Figure IV - 3. It was found that the higher temperature preparation was more active. The C3H/HeJ strain was much more sensitive than the CD-1 strain to the tumorigenic activity of the fumes. The simulated sunlight had an inhibitory effect on the rate of appearance of tumours and on the final tumour incidence. The ratio of tumour types expressed as a percentage between benign and malignant tumours were high for the C3H/HeJ groups with a ratio of 30:60 and much lower for the CD-1 groups at 33:5. The coal tar pitch fume materials showed effects that appeared to be consistent with their benzo[a]pyrene content compared to the benzo[a]pyrene controls. The petroleum asphalt fume material showed higher activity than would be expected based on their content of benzo[a]pyrene or of total polycylic aromatic hydrocarbons. This suggested the presence of other factors contributing to the tumorigenic response.

A chemical analysis of the petroleum asphalt material indicated that aliphatic hydrocarbons were the major components. The high aliphatic content of the asphalt fume sample is interesting in light of earlier studies (Horton et al., 1957, Bingham and Falk, 1969) which indicated that some alkyl hydrocarbons exhibit co-carcinogenic activity. Further characterization, fractionation and testing of these materials are needed in order to identify any indicator compound(s) for asphalt

FIGURE IV-3

Comparison of Generation Times Necessary to Produce Sufficient Roofing Material Fumes for an ED_{50} Tumorigenic Response in C3H/HeJ Mice



fume occupational exposure. These have been implicated in tumour-promoting characteristics. Substances such as thiophenes which are heterocyclic sulphur compounds as well as dihydrofuranones, heterocyclic oxygen compounds could possibly be initiating type substances in these mixtures.

The analysis of the coal tar fume products showed components that were largely aromatic in structure. By examining Figure IV - 3 which compares the tumorigenic responses of coal tar and asphalt roofing materials in C_3H/HeJ Mice, relative potencies can be derived at the two experimental temperatures. Using the total dosage of fumes for an ED_{50} as the most important indicator, at 232° C a relative potency of 2500/328 or 7.8/1 can be derived. Similarly at 318° C, a relative potency of 2050/165 or 12.4/1 has been observed. Taking the average of these two ratios gives a ratio of about 10/1, indicating that the coal tar is ten times more potent than asphalt in carcinogenic potential. Figures IV - 4 through IV - 13 represent the cumulative tumour incidence expressed as percent of the number of mice at risk at the appearance of the first tumour for the various experimental situations.

A summary of the effects of asphalt on animals is shown in Table IV - 8

TUMOR INCIDENCE

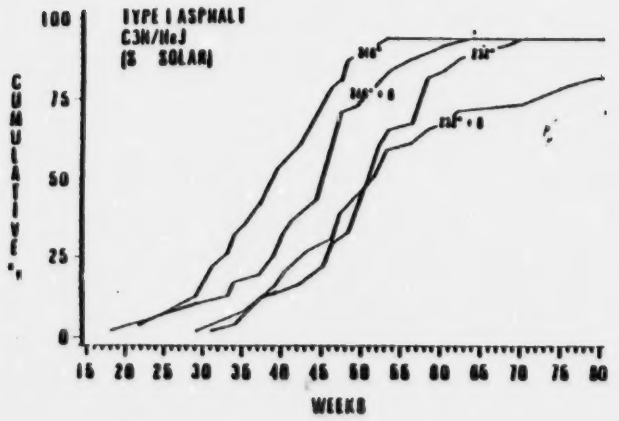


FIGURE IV-4

TUMOR INCIDENCE

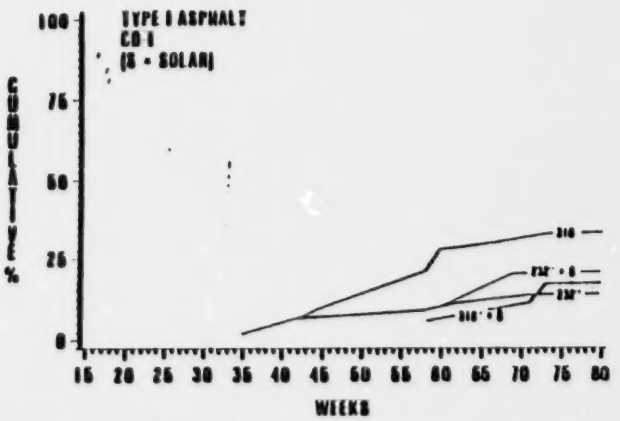


FIGURE IV-5

TUMOR INCIDENCE

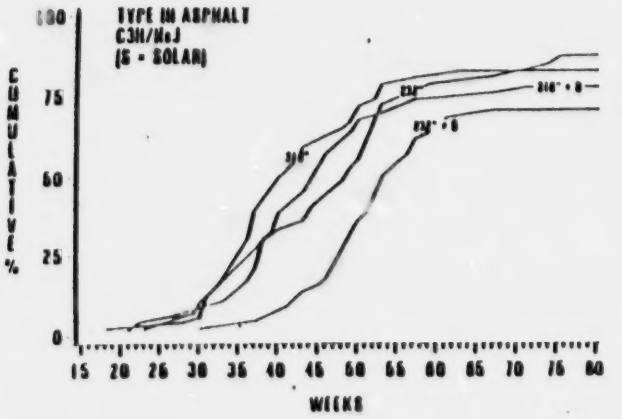


FIGURE IV-6

TUMOR INCIDENCE

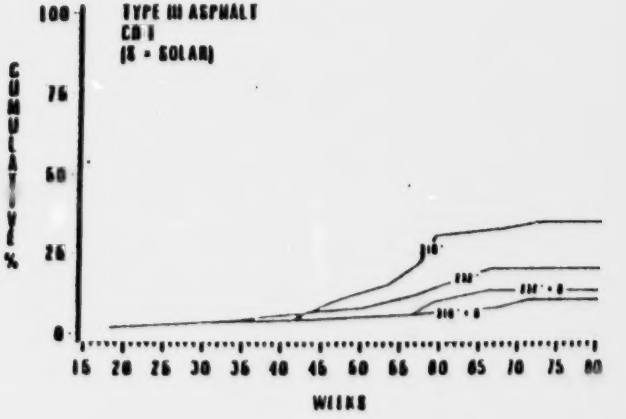


FIGURE IV-7

TUMOR INCIDENCE

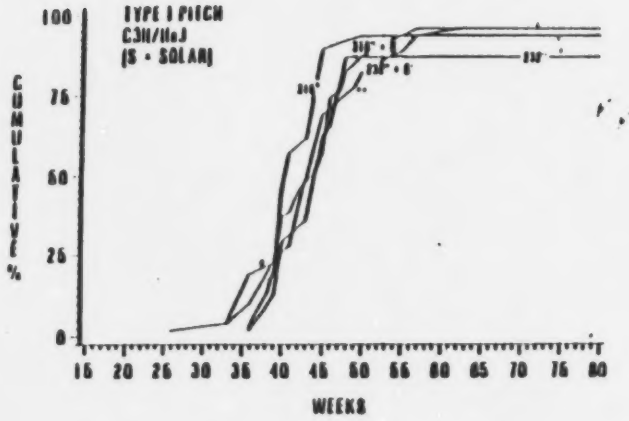


FIGURE IV-8

TUMOR INCIDENCE

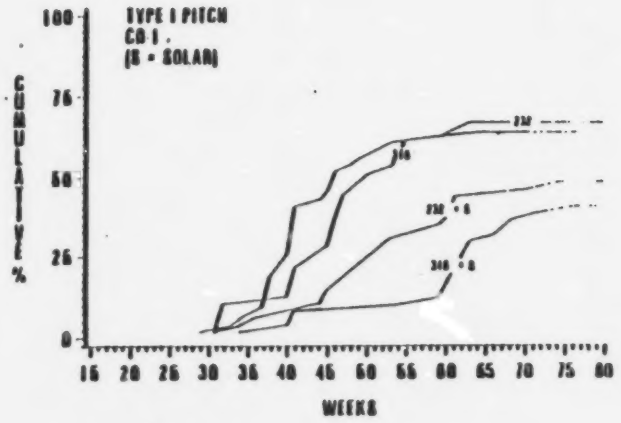


FIGURE IV-9

TUMOR INCIDENCE

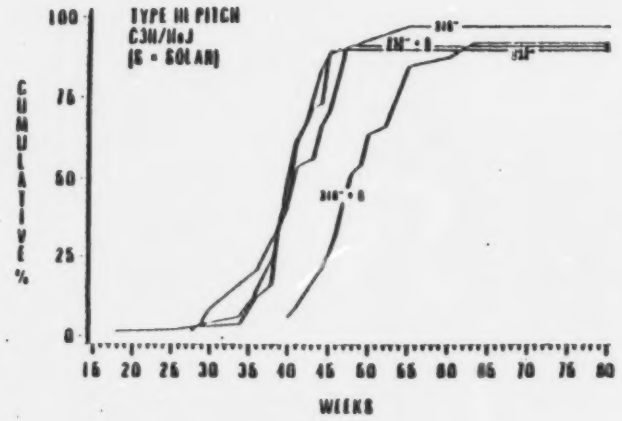


FIGURE IV-10

TUMOR INCIDENCE

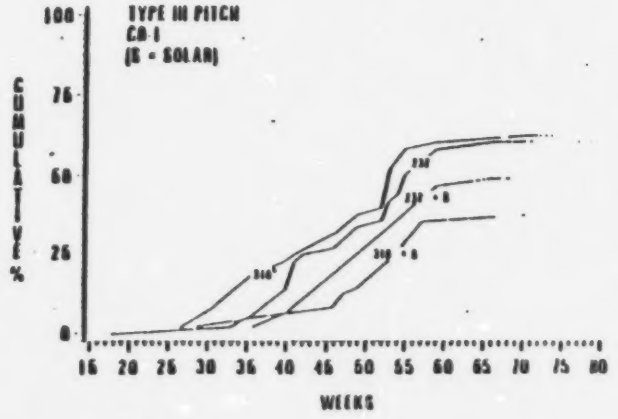


FIGURE IV-11

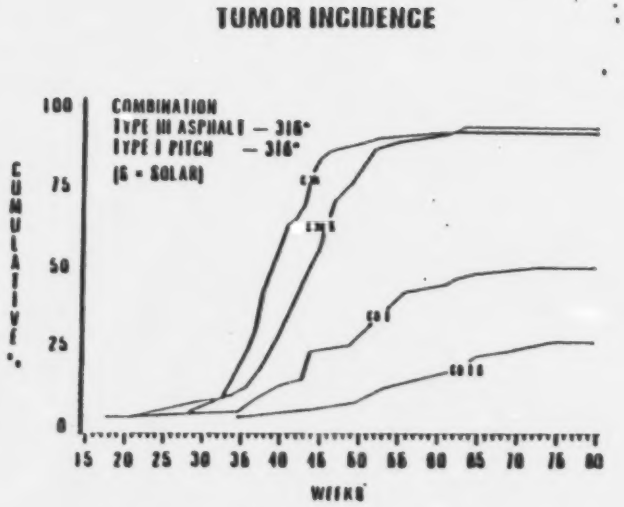


FIGURE IV-12

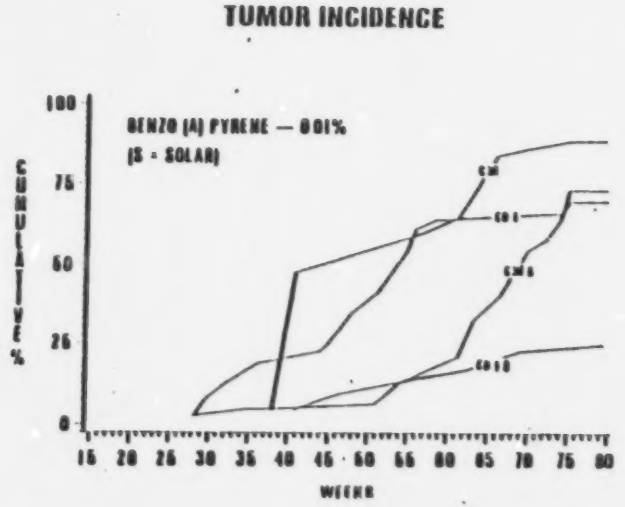


FIGURE IV-13

Appendix Figures IV-4 through IV-13 represent the Cumulative Tumor Incidence expressed as percent of the number of mice at risk at the appearance of the first tumor. All tumors used in these analyses were histopathologically confirmed. -S represents the solar light exposed groups.

Table IV - 8 Summary of the Carcinogenic Effects of Asphalt in Animals

Author/year	Exposed to	Exposure route, Concentration and Duration	Species	No. of Animals	Effects/Outcome
Simmers et al. 1959	Asphalt from Western U.S. crudes	Applied to skin, In benzene bi-weekly	Mice (C57 black)	68	12 carcinomas
Simmers et al. 1959	Asphalt from Western U.S. crudes	By injection, subcutaneously, 1% in olive oil 0.2 ml 2x/week 1x/week-41 weeks	Mice (C57 black)	33 m 29 f	8 sarcomas
Hueper and Payne 1960	Road Asphalt	Applied to skin, in acetone heated, 1 drop, bi-weekly 2 years	Mice (C57 black) and Rabbits	250	1 carcinoma and 2 papillomas
Hueper and Payne 1960	Roofing Asphalt	Applied to skin, in acetone heated, 1 drop, bi-weekly 2 years	Mice (C57 black) Rabbits	50 6	No cancer
Hueper and Payne 1960	Road Asphalt	By injection, thigh intramuscular, 50% in tricaprylin, 0.2 ml bi-weekly, 12 doses	Rats (C57 black)	120	13 sarcomas
Hueper and Payne 1960	Roofing Asphalt air blown flash	By inhalation, Vaporized at 250-275 deg F 5 hrs/ day 4 days/week	Guinea Pigs Rats (Bethesda black)	30 65	No cancers of skin or lungs
Simmers 1964	Asphalt from Western U.S.	By inhalation, aerosol in moist air 30 min/day 5 days/week 16-1/2 months	Mice (C57 black)	20	1 papillary adenoma
Simmers 1964	Asphalt from Western U.S. crudes	By inhalation, smoke from sample heated at 250 deg F 6-7-1/2 hr/day	Mice (C57 black)	30	1 bronchial adenoma, effects included patchy regions of emphysema, bronchiolar dilation, pneumonitis and severe local bronchitis was observed

cont'd

Table IV - 8
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Simmers et al. 1965b	Asphalt air refined	Applied to skin, heated 75-100 ag 1-3xweek - 2 years	Mice (C57 black)	50	1 papilloma
Simmers et al. 1965b	Asphalt air refined	Applied to skin, 9% toluene 20-30 ag - 3x/week 2 years	Mice (C57 black)	20	9 sarcomas
Simmers et al. 1965b	Asphalt steam refined	Applied to skin, heated 75-100 ag 3x/week, 1-1/2 years	Mice (C57 black)	63	3 sarcomas and 2 papillomas
Simmers et al. 1965b	Asphalt saturates and aromatics	Applied to skin, heated 33 ag 3x/week, 1-1/2 years	Mice (C57 black)	50	13 carcinomas and 13 papillomas
Simmers et al. 1965a	Asphalt from Western U.S. crudes	By injection, subcutaneously, heated 200 ag, single dose repeated after 4 months	Mice (C57 black)	25 m 25 f	3 sarcomas
Simmers et al. 1965a	Asphalt from Western U.S. crudes	By injection, subcutaneously, heated 200 ag, single dose repeated after 3 months, 9 days	Mice (C57 black)	25 m 25 f	No sarcomas
Mallcave et al. 1971	Road Paving Asphalts	Applied to skin, 10% in benzene, 25 ul, bi-weekly	Mice (Swiss)	218	1 carcinoma and 5 papillomas, amyloidosis of spleen and kidney was also observed
Emmett et al. 1981	Standard asphalt from roofing operation	50mg (50% toluene) to the intra-scapular shaved skin of mice, bi-weekly for 80 weeks	Male Mice (C3H/HeJ)	50	No tumours

cont'd

Table IV - 8
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Niemeier et al. 1985	Roofing petroleum-asphalts and coal tar pitches	Applied to skin, volatile fume at 232 and 316 deg C with sunlight bi-weekly, 18 months or without sunlight	Mice (CD-1 and C3H/HeJ)	160	Malignant tumours were high for the C3H/HeJ groups with a ratio of 30:60 and much lower for the CD-1 groups at 33:5, sunlight had an inhibitory effect on the rate of appearance of tumours. Petroleum asphalt fumes materials showed higher activity than expected. Relative tumorigenic potency of coal tar was approximately ten times that of asphalt.

4.2 Mutagenicity Studies

4.2.1 Mutagenicity - Coal Tar Pitch

Rao et al., (1979) found that a dimethyl-sulphoxide extract of coal tar pitch was mutagenic in S. typhimurium TA1537, TA98 and TA100 in the presence of Aroclor-induced rat-liver metabolic system (S9). Claxton and Huisingh (1980) and Nesnow and Lewtas (1981) found that dichloromethane extracts of emissions from roofing tar pots were mutagenic in S. typhimurium TA1537, TA1538, TA98, and TA100 in the presence of (S9). No activity was observed in strain TA 1535. The same material was tested further in a number of other test systems by Casto et al., (1981); Curren et al., (1981); and Mitchell et al., (1981). The extract did not produce mitotic recombination nor DNA fragmentation in primary Syrian hamster embryo cells. The extract was mutagenic in BALB/C3T3 cells and was positive in the L5178 Y mouse lymphoma system both in the presence and absence of S9. In contrast it was negative in Chinese hamster ovary (CHO) cells in the absence of S9. The extract induced significant increase in the frequency of sister chromatid exchanges in CHO cells both in the presence and absence of S9. An observed increase in morphologically transformed foci in the BALB/C3T3 cells was not statistically significant when tested either in the presence or absence of S9. A significant enhancement of viral transformation was observed in Syrian hamster embryo cells.

4.2.2 Mutagenicity - Coal Tar

Saperstein and Wheeler (1977) evaluated each of four therapeutic preparations of coal tar for mutagenicity in Salmonella typhimurium TA98 in the presence of Aroclor-induced rat-liver metabolic system (S9). Three of the 4 coal tar shampoos tested as hexane extracts were mutagenic in S. typhimurium TA100 but not in the presence of S9 in a study by Fysh et al., (1980). The shampoo with the highest activity contained approximately 50 times more benzo[a]pyrene than the one that was negative.

4.2.3 Mutagenicity - Creosote

Simmon and Poole (1978) tested creosote in a coal tar and creosote mixture for mutagenicity in bacteria and in cultured mammalian cells. Both compounds were mutagenic in S. typhimurium TA1537, TA98 and TA100 in the presence of S9. No activity was observed in the absence of S9 or in strain TA1535. No mutations in E. coli strain WP2 were found. A positive concentration of related response in the L5178Y mouse lymphoma cell system in the presence of S9 was found. A much higher concentration was required to induce a positive response in the absence of S9 in experiments by Mitchell and Tajira (1978). Bos et al., (1983) reported positive results for creosote and S. typhimurium TA 1537, TA1538, TA98 and TA100 in the presence of S9. The

strongest responses were obtained with strains TA98 and TA100. In strain TA1535 no activity was observed. Fractions of PI creosote separated by thin layer chromotography were also mutagenic in S. typhimurium T98 in the presence of S9. This was reported by Bos et al., (1984). As well, the urine of rats administered creosote type PI (purchased from Cinda Chemicals BV, Uithoorn, The Netherlands; chemical structure of the mutagen(s) present in creosote PI is not given) with a dose of 250 mg per kg body weight, was found to be mutagenic in S. typhimurium TA98 and/or TA100 when tested in the presence of B-glucuronidase and S9 or with B-glucuronidase only.

4.2.4 Mutagenicity - Coke Oven Emissions

Claxton (1981) reported the topside coke-oven sample was mutagenic to Salmonella typhimurium strains TA98 and TA100 both with and without an exogenous metabolic system. Junger et al., (1981) tested a series of other topside coke-oven samples taken from the same coke battery which were also reported to be mutagenic to strain TA98 with and without metabolic activation. Furthermore, the mutagenicity of these samples was not affected by the electric charge on the electrostatic precipitator in the sampler. Albert et al., (1983) examined another coke-oven main sample and found that it was also mutagenic to strain TA98 both with and without the metabolic system. Both coke-oven main and topside coke-oven samples showed increased mutagenicity in the

presence of metabolic activation in strain TA98. Moreover, both samples induced sister chromatid exchange in Chinese hamster ovary cells with and without metabolic activation (Mitchell et al., 1980, 1981; Albert et al., 1983).

4.2.5 Mutagenicity - Asphalt

Penalva et al., (1983) found that an extract of road-coating tar in dimethylsulphoxide was mutagenic to S. typhimurium TA98 in the presence of Aroclor-induced rat liver metabolic system S9. Vapours, particles and aerosols admitted at 550° C, 350° C, and 250° C were also weakly mutagenic both in the presence and absence of S9 and S. typhimurium TA98 and/or TA100.

4.3 Summary

Review of the experimental animal studies of coal tar products including coal tars, creosotes, creosote oil, anthracene, anthracene oil, and coke oven main, provide strong evidence of carcinogenicity in animals (IARC Category 1 for animal carcinogenicity). Short term tests for mutagenicity confirm that these products are capable of producing mutations and hence exhibit genetic activity. The evidence for the animal carcinogenicity of asphalt is convincing; however, it does not equal the potency of coal tar-derived products (IARC Category 1 for animal carcinogenicity). Short term biological tests

demonstrate genetic activity of petroleum products, however, the evidence is not as extensive.

The experiments by Niemeier (1985) indicate that there is a greater occupational hazard from exposure to asphalt fumes than that summarized by NIOSH in 1977. Exposure to asphalt fumes significantly increases carcinogenic risk, and this risk increases further with higher temperatures. The B[a]P content of coal tar pitch fume materials can be used as a satisfactory indicator of carcinogenic activity but not for asphalt fume materials. The presence of aliphatic hydrocarbons may be responsible for co-carcinogenic activity of the asphalt.

From figure 3 of that study, it is evident that the effective dose of condensed asphalt fumes to produce a 50 percent skin tumor incidence in male C3H/HeJ mice was approximately 10 times higher than that of condensed coal tar fumes. The actual figures used in the averaging process were 7.8 (2500/320) for the low temperature fumes and 12.4 (2050/165) for the high temperature fumes. These estimates are largely empirical and may not ultimately reflect the true human cancer risk when suitable human epidemiological data becomes available, if ever. The rating of the evidence for carcinogenicity in experimental animals according to the International Agency for Research on Cancer (IARC) would be category 1 based on evidence of carcinogenicity in multiple strains of mice (C3H/HeJ and Swiss CD-1) and in multiple experiments (see section 4.1.5 and Appendix II).

It was estimated that by maintaining proper heating con-

ditions for the kettle, the carcinogenic risk could be reduced by a substantial degree, an approximate 7 to 14 fold theoretical decrease for coal tar pitch and asphalt, respectively. The potential for interaction of the two types of substances are possible but were not measured directly. It is important to note that Bingham and Falk (1969) have demonstrated that co-carcinogens of the aliphatic type have their most noticeable effect when the concentration of carcinogen is low.

The relative potency of coal tar pitch and asphalt of paramount importance in performing a risk assessment and are explored further in Chapter 7.

CHAPTER FIVE

REPRODUCTIVE EFFECTS

5.1 Coal Tar Pitch and Related Complex Mixtures

There has been no research in humans and very little in other species concerning the reproductive effects of exposure to coal tar pitch and related complex mixtures.

In neonatal rats, Bickers et al., (1982) assessed the effects of a therapeutic coal tar preparation and certain of its chemical constituents, including benzo[a]pyrene, on liver and skin aryl hydrocarbon hydroxylase (AHH) activity. AHH, a cytochrome P450-dependent monooxygenase, plays an important role in the metabolism of polycyclic aromatic hydrocarbons.

Application of 100 ml of coal tar solution (USP) to neonatal rats 24 hours before sacrifice resulted in 15- and 18-fold increases in skin and liver AHH, respectively, relative to control values. This result was observed, despite evidence in the study that coal tar fumes had contaminated the control animals.

In addition, coal tar solution was applied to the shaved backs of pregnant rats 48 hours before the expected date of delivery. Treated mothers manifested a 3.8- and 4.8-fold increase in skin and liver AHH activity, whereas exposed fetuses

had corresponding values of 2.0 and 1.9.

With respect to benzo[a]pyrene per se, its application to neonatal rats resulted in 9- and 8-fold increases in AHH activity in skin and liver respectively, relative to control animals.

These data showed that coal tar application (and even contaminating exposure to coal tar vapours in control animals) readily resulted in AHH induction in skin and liver of neonatal rats. The induction of AHH activity in prenatal liver and skin, following application of coal tar to pregnant animals, demonstrates that coal tar or its metabolites are capable of traversing the placenta in the rat. The significance of these findings is that AHH activity is suspected to be associated with the reproductive toxicity of polycyclic aromatic hydrocarbons, as discussed in more detail subsequently.

The findings in a preliminary study reported by Bacelar (1932) were inconclusive with respect to ovarian changes in rabbits painted with tar. Few animals were studied, little methodological detail was given and the report of the final results, if published, has not been found.

Schultz et al., (1982) have studied the embryotoxic and teratogenic effects of aqueous extracts of tar from a coal gasification electrostatic precipitator.

Embryos of the amphibian, Xenopus laevis, of mid-blastula to late-blastula stage, were studied in groups of 50. The tar extract was prepared by the heating of 8 ml of tar at 60° C, followed by cooling through application to the lower surface of a

125 ml flask; 60 ml of dechlorinated tap water was added and the sample was stirred for 16 hours at ambient temperature. A graded concentration series was formed by appropriate dilution to a volume of 200 ml, with dechlorinated tap water. The gasifier tar was separated into chemical classes, including basic and acidic components, as well as neutral materials which were separated into aliphatic, aromatic, polyaromatic, and polar fractions, by methods described in the text. In addition, elemental composition, with respect to carbon, hydrogen, nitrogen, and sulphur, was determined. Further, mass spectrometry was used to characterise the organic components of the extracts.

The results showed a direct linear correlation for the relationship of concentration to mortality, with an LC_{50} of 0.83%.

Morphologically normal embryos exhibited considerable growth reduction with increasing concentration. Motility reduction and, to a lesser extent, alterations in pigmentation were also found to vary with concentration. Mean total severity of abnormalities in embryos, as well as number of abnormal embryos, showed a direct relationship to concentration. The abnormalities showing the clearest dose response were optic and spinal malformations.

The major organic components of the extracts included low molecular weight phenols, furans, aromatic hydrocarbons, and nitrogen-containing aromatics. Based on prior investigations by the authors into the effects of coal-gasification sour water on

Xenopus embryos, the observed embryotoxicity was thought to be caused mainly by the phenols. However, no hypothesis was offered in terms of the agents responsible for the observed teratogenic effects.

Subsequently, this group of investigators, Dumont et al., (1983), has proposed the "frog embryo teratogenesis assay; Xenopus" (FETAX), as a short-term assay applicable to complex environmental mixtures. They have developed a "teratogenic index", consisting of the ratio of the 96 hour LC_{50} to the 96 hour EC_{50} (the concentration that induces terata in 50% of surviving embryos). Additional details and guidelines for interpretation are given in the text.

A number of fossil-fuel samples were tested in the system: a coal-derived fuel oil blend; a shale-derived crude; a coal-gasifier electrostatic-precipitator tar; and an aromatic and an aliphatic natural petroleum crude. The preparation of aqueous extracts of these samples and the experimental methods were essentially the same as those described in the study of Schultz et al., (1982).

The most severe embryotoxicity was associated with the coal-derived fuel oil blend and the coal-gasifier electrostatic-precipitator tar, with LC_{50}s of 1.48% and 0.83% respectively. The shale-derived crude had an LC_{50} of 6.97%. Very little toxicity was observed for the petroleum crude extracts.

The greatest teratogenicity was also associated with the coal-derived materials, with EC_{50}s of the same order of magnitude

as those found for the LC_{50}s. In these instances the closeness of the LC and EC values suggests that the potential absolute level of teratogenicity may be 'masked' by embryotoxicity. The teratogenic index was highest for the shale-derived crude, with a value of 2.07.

Growth was most severely reduced by the coal-derived materials and the coal-derived fuel oil blend was the most potent inhibitor of development. The shale crude had little effects on growth, although development was markedly retarded. The petroleum products manifested little effect on development, although growth reduction was associated with the aromatic petroleum crude. Pigmentation and motility were also reduced by the coal- and shale-derived materials.

In addition, this investigation revealed that specific types of teratogenic effects in the embryos could be delineated in association with the particular types of material studied. That is, on the basis of the appearance of the embryo, it was felt possible to identify the responsible teratogen.

In these five samples, the total carbon content was essentially the same. Nevertheless, the content of aromatic carbon was highest in the coal-derived materials, while the hydrogen content, also reflecting aromaticity, was lowest in these samples. In addition, these samples had the highest oxygen content, an indication of acidic components. The presence of phenol and traces of carboxylic acids, was confirmed by gas chromatography/mass spectrometry. In aqueous extracts, these

compounds would occur in relatively high concentrations. Again the authors state, based on their earlier observations (not cited in their paper), that phenols are probably responsible for the embryotoxicity of these materials. The shale-derived crude and the coal-gasifier electrostatic-precipitator tar had the highest nitrogen content, an indication of aromatic amines and azaarenes; the authors cite earlier investigations that they have conducted demonstrating the teratogenicity of these compounds.

The petroleum crude extracts were similar in composition, dominated by neutral components including benzenes, naphthalenes and thiophenes.

In an abstract also published in 1983, Dumont et al. restate the finding that extracts of the coal-gasifier crude tar appear more embryotoxic than teratogenic (teratogenic index 1.07). However, they report that when the tar was extracted with DMSO, highly teratogenic materials appear to have been solubilized, as the teratogenic index increased to 4.47. Natural petroleum crudes again showed little teratogenic activity.

The polyaromatic shale fraction was found to be highly teratogenic (teratogenic index 37.68), while that of the tar was associated with more embryotoxic effects (teratogenic index 1.30). On the other hand, the teratogenic index associated with mono- and diaromatic class fractions of the tar was higher (5.24) than similar fractions from shale (3.37). No direct correspondence was found with mutagenicity data, suggesting that different compounds in these mixtures may account for their

mutagenicity and teratogenicity.

Stoker et al., (1985) studied certain reproductive effects of coal-derived tars on selected aquatic and mammalian organisms.

A solvent-refined coal-heavy distillate (boiling point range 260°-450° C), was studied in female C-1 mice. The distillate was administered to the mice in solution with corn oil. Ten mice were assigned to each of four treatment groups receiving 250, 500, 1,000, and 2,000 mg/kg, and to one control group. A maximum tolerable dose was defined as the lowest concentration causing toxicity. Treatments were administered orally by gavage for eight consecutive days. Subsequently, pregnant mice were treated at the maximum tolerable dose (determined to be 750 mg/kg), for eight consecutive days beginning on the 7th day of gestation. Twenty animals were assigned to the treatment group and to the control group respectively.

While there was no statistical difference in number of implantations between treatment and control groups, distillate treatment was associated with a reduction in the number of viable litters and the number of pups, as well as with a decrease in average litter weight. Occurring as early as the second day of dosing and periodically throughout gestation, vaginal bleeding was noted in 50% of the treated mice. Of those found to be bleeding only three mice delivered and of these only one litter was in the normal size range of the controls. There was also a delay of 12 to 25 hours in parturition in the treated group relative to the controls.

In addition, cutthroat embryos (Salmo clarki) were exposed to the coal-heavy distillate, (described above), from 17 hours of age, at concentrations of 0, 6.25, 12.5, 25, 50, and 100 ppb in a circular flow-through mini-diluter. At day 12 all embryos had hatched; however, abnormalities were present, including erosion of fins and deficient vascularization of the yolk sac. Following 30 days post-hatching, the fish were weighed and measured. An inverse relationship was found between weight and size and distillate concentration; those exposed at the highest levels had extensive fin erosion. At the end of the study, all fish exposed to 100 ppb had died.

The above text summarizes the literature on the reproductive effects of coal tar-related substances which has been identified and assembled to date. While these data consistently indicate dose-related reproductive effects, it is difficult to make extrapolations to human exposure conditions because of differences in species and route of administration.

5.2 The Instance of Benzo[a]pyrene

Polycyclic aromatic hydrocarbons, a toxicologically significant group of chemicals, are important constituents of coal tar pitch; benzo[a]pyrene is one of the most widely studied members of this group. It is worthwhile to review briefly the literature concerning what is known of the association between benzo[a]pyrene exposure and adverse reproductive outcomes. To do

this for each of the numerous polycyclic aromatic hydrocarbons of importance in coal tar pitch is beyond the scope of this document. However, consideration of the role played by benzo[a]-pyrene will shed some light on the concerns of this chapter.

5.2.1 Metabolic Considerations

Numerous studies have investigated benzo[a]pyrene metabolism as it pertains to reproductive toxicity. Considered here are the metabolic roles played by the pregnant female, the placenta and the fetal liver. The issue of benzo[a]pyrene conversion in end-organs - .e.g, testis, ovary, mammary gland, uterus - is considered below in discussion relating to each of these sites.

Oxidative conversion of polycyclic aromatic hydrocarbons results in the formation of electrophilic metabolites such as epoxides and diolepoxides, which readily react with macro-molecules in tissues, forming covalent bonds. The enzyme systems responsible for this metabolic processing to reactive intermediates are widely distributed in the body, including the gonads (Mattison et al., 1983). More than 20 different metabolites result from the metabolism of benzo[a]pyrene by the mixed function oxidase, aryl hydrocarbon hydroxylase (AHH) (Gelboin, 1980).

Clearly, the time of development of significant AHH activity in the placenta and fetal organs has implications for the potential reproductive toxicity of benzo[a]pyrene. In addition,

benzo[a]pyrene metabolism in the pregnant female is relevant, as placental transfer of benzo[a]pyrene is known to occur (as discussed further below). Especially important is the potential role of induction of AHH activity by exposure to benzo[a]pyrene or other polycyclic aromatic hydrocarbons.

Lin et al., (1976) studied the quantities of benzo[a]pyrene metabolites in the maternal liver and blood of mice and rats subsequent to a single oral administration of 40 mg/kg benzo[a]-pyrene on day 6, 8, 12, or 15 of pregnancy. It was found that these amounts were highest following treatment on day 15, indicating increasing metabolic capacity as pregnancy progresses. Increasing enzyme activity in the placenta may in part account for this change in capacity.

Juchau (1971) treated rats on day 15 of pregnancy with a polycyclic aromatic hydrocarbon, 3-methylcholanthrene. A peak in placental AHH activity was found on days 17 to 19 of pregnancy; without such pretreatment, placental enzyme activity was low. Similarly, Gillette et al., (1973) found that without pretreatment AHH activity in the fetal rabbit liver was low.

Other investigators demonstrated that pretreatment resulted in a 30-fold increase in AHH activity in the maternal rat liver, compared to 11- and 12-fold increases in the placenta and fetal liver respectively (Bogdan and Juchau, 1970). Welch et al., (1972) demonstrated that induction of AHH activity in the fetal rat liver required a 40-fold higher dose of benzo[a]pyrene than such induction in maternal liver. Nonetheless, AHH-inducibility

may exist from a very early embryonic age: benzo[a]pyrene metabolites, following induction by tetrachlorodibenzodioxin, have been detected in cultured 3-1/2 day mouse embryos, particularly in responsive strains (Filler and Lew, 1981).

Juchau (1971) has demonstrated certain biochemical similarities between rat and human placental AHH, suggesting the suitability of the rat model for study. One of these similarities is inhibition of AHH by estrogens, which may counter developmental increases in AHH activity with the advancement of pregnancy.

Numerous studies have investigated human placental AHH activity; only certain of these are referred to here. This considerable interest arose from the finding that benzo[a]-pyrene could be hydroxylated by human placental tissues (Welch et al., 1968; Nebert, 1974). In human placentae, AHH activity increases with the advancement of pregnancy. Goto and Wiebel (1980) found AHH activity to be highly inducible in human primary amnion cell cultures, derived from the placenta at term in healthy women; they have proposed such cultures as models for the study of placental metabolism of substances by AHH.

It has been amply shown that AHH activity is induced by maternal smoking (Juchau, 1973), being far higher in the placentae of smokers than those of non-smokers. In smokers, detectable levels appear as early as 11 weeks of gestation (Juchau, 1971).

Little is known concerning the extent to which reactive

intermediates formed by benzo[a]pyrene metabolism may be inactivated by further metabolic processes. In addition, it is not clear to what degree inhibition of AHH by the increasing estrogen and progesterone levels with advancing pregnancy may be protective (Juchau, 1971).

Some controversy has surrounded the issue of the spectrum of products formed by placental metabolism of benzo[a]pyrene, particularly with respect to the proportions of phenols and diols produced. Namkung and Juchau (1980) demonstrated that the quantity of diols in the metabolite profiles depends on the initial substrate concentration. The significance of these results is that benzo[a]pyrene-7,8-diol produced in the placenta may reach the fetus, where conversion may occur to the highly reactive 7,8-diol-9,10-epoxide.

In addition to the placenta, AHH activity is found in human fetal tissues, particularly the liver, kidney and adrenal gland (Pelkonen et al., 1971; Juchau et al., 1972). In fetuses of eight to 26 weeks gestation, AHH activity levels in fetal liver exceed those in placenta, but show little tendency to increase with gestational age (Pelkonen et al., 1971). Compared to that of adult liver, AHH activity in fetal liver is low (Rane et al., 1973; Pelkonen et al., 1973). Nonetheless, in human fetal liver, AHH activity has been detected as early as six to seven weeks gestation in abortuses from both non-smokers and smokers, by Pelkonen and Karki (1973); at five to eight weeks gestation, AHH activity was not detected in the placenta.

Thus, while placental capacity to metabolise benzo[a]pyrene does not develop until 11 to 13 weeks gestation in smokers and remains low in non-smokers, fetal liver manifests this capacity from an earlier stage of gestation, with no apparent relationship to maternal smoking. The degree to which benzo[a]pyrene metabolites generated in or transmitted to the fetus may be associated with toxic responses is not fully understood.

5.2.2 Mutagenicity Considerations

Microsome preparations from the placentae of smokers, but not those of non-smokers, have been found to catalyse the formation of benzo[a]pyrene metabolites which produced mutagenic effects in Salmonella typhimurium (Jones and Juchau, 1977). Capacity for catalysis of covalent binding of benzo[a]pyrene metabolites to DNA has been shown to vary directly with the AHH activity of placentae (Barry et al., 1977; Vaught et al., 1979).

Indices of mutagenic effects of benzo[a]pyrene metabolites in embryo cell cultures constitute another source of inference about what may occur in vivo. Sebti et al., (1985) have demonstrated the formation of benzo[a]pyrene:DNA adducts in embryo cell cultures from mice, rats and hamsters, following as little as five hours of exposure to a benzo[a]pyrene-containing medium.

Galloway et al., (1980) used the sister chromatid exchange assay to study the metabolism of benzo[a]pyrene by cultured mouse

embryos explanted at 7-1/2 or 8-1/2 days of gestation. In species known to generate, upon exposure, the capacity to metabolise polycyclic aromatic hydrocarbons, a high frequency of sister chromatid exchange was observed upon culture in medium containing benzo[a]pyrene. Little or no increase in sister chromatid exchange was noted in "non-responsive" strains. The same group of investigators, Pedersen et al., (1985) again used the sister chromatid exchange assay as an index of benzo[a]pyrene metabolism in mouse morulae, blastocysts, and embryonic and extraembryonic tissue layers. Increases in sister chromatid exchanges were observed in tissues of both embryonic and extra-embryonic lineages upon benzo[a]pyrene treatment of "responsive" 7-1/2 and 8-1/2 day embryos. The results suggest that AHH activity may occur in most or all tissues of early mammalian embryos; consequently, activation of polycyclic aromatic hydrocarbons reaching the conceptus could occur at the time of morphogenesis and organogenesis.

Another form of mutagenic response has been observed by Basler and Rohrborn (1976) in their study of chromosome aberrations in oocytes of NMRI mice. Oral administration (450 mg/kg) of benzo[a]pyrene was associated with an aberration frequency of 9% in oocytes in the experimental group, relative to 1% in the control group. As is noted below in the discussion of ovotoxicity of benzo[a]pyrene, this response may well be dependent upon metabolic activation within the ovary.

5.2.3 Effects on Estrous Cycle, Uterus and Ovary

A limited amount of research in animals has been devoted to the effects of benzo[a]pyrene on the estrous cycle and uterine and ovarian responses.

Rigdon and Rennels (1964) studied the response of the rat estrous cycle to benzo[a]pyrene in the diet (1 mg/kg of food). No effects attributable to this exposure were observed.

Payne (1958) injected female rats intraperitoneally with a single dose of 10 mg of benzo[a]pyrene, studying them histologically 12 months later. Considerable hyperplasia was noted in the uteri and the ovaries manifested cystic changes with greatly reduced numbers of normal follicles.

The latter results of this early research are consistent with the demonstration by Mattison and Thorgeirsson (1979) of destruction of murine oocytes by polycylic aromatic hydrocarbons. Significant strain differences in sensitivity to oocyte destruction were observed, generally paralleling differences in metabolic activation.

Shiromizu and Mattison (1982) investigated the site of metabolic processing of polycyclic aromatic hydrocarbons that is associated with ovotoxicity. Mice were treated with bilateral or unilateral intraovarian injections of benzo[a]pyrene. It was found that unilateral injection was associated with destruction of oocytes only in the treated ovary. In the contralateral ovary, treated only with corn oil, no effect was observed on

oocyte number. These data were consistent with the existence of metabolic capacity within the ovary to generate reactive ovotoxic intermediates. The toxic mechanism is thought to involve either direct oocyte destruction or toxicity to granulosa cells that support the oocyte in the follicle (Mattison and Ross, 1982). However, it should be noted that although ovarian AHH activity has been shown to be necessary for oocyte destruction by polycyclic aromatic hydrocarbons, it appears to account for little of the differences in the extent of ovotoxicity observed between different strains.

Additional work by these investigators and others (Mattison et al., 1983) has focussed on the metabolic pathways for activation of polycyclic aromatic hydrocarbons within the ovary. The results indicate that metabolic processing of benzo[a]pyrene in the 7,8,9,10-region may constitute a more valid measure of the role of metabolic activation in oocyte destruction.

5.2.4 Testicular Effects

The testicular effects of benzo[a]pyrene exposure in animals have been studied by a few investigators.

Payne (1958) administered single intraperitoneal injections of 4 mg of benzo[a]pyrene to 6 month old rats. Twelve months later (or at time of illness or tumour appearance, if earlier), histological examination was conducted. In three of 30 males in the experimental group, interstitial cell tumours were iden-

tified; none were observed among control animals. In the remaining treated males, interstitial tissue was completely absent; a high proportion of animals showed atrophy of the seminiferous tubules, with an absence of spermatids and spermatazoa.

The effects of benzo[a]pyrene on the morphology of sperm in mice have been studied by Wyrobek and Bruce (1975). Five daily intraperitoneal injections of 20 or 100 mg/kg were administered. Morphology was examined at 0, 4 and 10 weeks following exposure, corresponding to exposure of developing spermatids, spermatocytes and spermatogonia, respectively, to benzo[a]pyrene. At the higher dose, morphological abnormalities were observed in 15 to 20% of sperm at four and ten weeks post-exposure; some excess mortality was observed in this exposure group. At the lower dose, no increase in abnormality rate over the control rate of 1 to 3% was observed.

The "blood-testis" barrier - between the testicular interstitial compartment and the seminiferous tubules - most effectively limits access to developing sperm by large hydrophilic molecules; however, access by lipophilic substances like polycyclic aromatic hydrocarbons appears not to be significantly impeded (Okumura et al., 1975; Setchell and Main, 1978). Nevertheless, in the interstitial compartment, the testis has complete enzymatic systems capable of metabolizing of polycyclic aromatic hydrocarbons to reactive intermediates, as well as some capacity for detoxification of these metabolites

(Dixon and Lee, 1980). Thus, activation of polycyclic aromatic hydrocarbons to reactive intermediates is unlikely to occur to a significant degree within the seminiferous tubule. The blood-testis barrier may function to reduce access to the developing sperm by the hydrophilic products of metabolism. Lee and Nagayama (1980) have demonstrated that testicular metabolism of benzo[a]pyrene yields metabolites largely in the 7,8,9,10-region - a portion of the molecule thought to be significant in the formation of the highly reactive 7,8-diol-9,10-oxide.

5.2.5 Effects on Fertility

A number of researchers have investigated the antifertility effects of benzo[a]pyrene.

Rigdon and Rennels (1964) and Rigdon and Neal (1965) studied the effects of dietary benzo[a]pyrene (0.25 to 1.0 mg per gram of food) on the fertility of male mice, the fertility of female mice, and on reproduction when both males and females were treated. Their results, however, permit few conclusions, as the sample sizes were small, there was no consistent use of control animals, there was little evidence of dose-response effects, and fertility was suspiciously low even among the control animals that were included.

In a study of dominant lethal effects in the mouse, Epstein et al., (1972) administered 500, 750 or 1,000 mg/kg of benzo[a]-

pyrene intraperitoneally to male mice, doses which were associated with approximately 10% mortality. Three and 8-week mating periods were used. Evidence was found of a treatment-related decrease in pregnancy rate, a decrease in number of implants per pregnancy, and an increase in early embryonic deaths. However, the investigators themselves noted a lack of consistency among the experiments in terms of magnitude of effect observed and the variables affected.

Mice exposed prenatally to benzo[a]pyrene have been demonstrated to have substantially reduced fertility (MacKenzie et al., 1979). This study is discussed further below, in the context of benzo[a]pyrene-associated teratogenicity.

To this point, relevant considerations concerning metabolism and mutagenesis, as well as effects on the estrous cycle, gonads and fertility, have been reviewed with respect to the reproductive toxicity of benzo[a]pyrene. To follow is a discussion of toxicological events occurring after conception - transfer across the placenta and mammary gland, embryotoxicity, fetotoxicity, teratogenicity, and transplacental carcinogenesis.

5.2.6 Transfer Across Placenta and Mammary Gland

Placental transfer of benzo[a]pyrene was studied by Raimondi and Pagani (1967). Pregnant rats were injected with tritiated benzo[a]pyrene, in oil-based and water-soluble vehicles from day 3 of pregnancy onwards. Throughout gestation detectable

radioactivity levels were documented in the fetuses. Kelman and Springer (1982) measured the clearance of radio-labelled benzo-[a]pyrene across the hemochorial placenta of guinea pigs, at 60 days of gestation. These investigators isolated the fetal circulation of the placenta, injected benzo[a]pyrene into the maternal circulation, and determined benzo[a]pyrene concentrations in the perfusate. It was found that benzo[a]pyrene, when introduced directly into the maternal circulation, gained easy access to the fetus. It was considered unlikely that appreciable amounts of benzo[a]pyrene metabolites were entering the fetal circulation and that a large fraction of the measured radio-labelled material was unmetabolized benzo[a]pyrene. However, additional research concerning placental transfer, using oral or dermal routes of administration and investigating transfer of metabolites is warranted.

Raimondi and Pagani continued administration of radio-labelled benzo[a]pyrene after delivery of the litters and observed increasing levels of radioactivity in pups suckled by dams given benzo[a]pyrene in water-soluble complexes; this finding suggested transfer into the milk. Quantitatively, West and Horton (1976) found that the transfer of dietary benzo[a]-pyrene to maternal milk is low in the sheep and rabbit (0.01% and 0.003% of dietary benzo[a]pyrene, respectively, found in the milk). In the milk, benzo[a]pyrene was found to be predominantly in the fat compartment. In this regard, it is of interest that Ritter and Malejka-Giganti (1982) found that the mammary gland

of rats was capable of the metabolism of benzo[a]pyrene and responsive to pre-treatment of lactating rats with 3-methylcholanthrene. However, the degree to which benzo[a]pyrene metabolites (for example, originating from the maternal liver) may be transmitted to milk remains poorly understood.

5.2.7 Embryotoxicity, Fetotoxicity and Teratogenicity

Numerous investigators have studied the embryotoxic, fetotoxic and teratogenic effects of benzo[a]pyrene.

Rigdon and Neal (1965) studied the effects of dietary benzo[a]pyrene in other mice; and observed no evidence of infertility, embryotoxicity or teratogenicity, however, because of lack of a control group and methodological limitations from conclusions are not possible. In rats, Rigdon and Rennels (1964) found that exposure to dietary benzo[a]pyrene was associated with reduced fertility, fetal resorption and fetal malformation; however, the small sample size limits the drawing of conclusions.

Wolfe and Bryan (1939) administered 5 mg of benzo[a]pyrene subcutaneously to pregnant rats on a daily basis. Upon sacrifice between day 10 and day 18 of pregnancy, no effect on implantation was noted, but fetal resorption was occurring with associated placental bleeding.

MacKenzie et al., (1979) administered benzo[a]pyrene orally to mice at doses of 10, 40 or 160 mg/kg per day, on days 7 to 16

of pregnancy. At the highest dose level, delayed ossification of the fetal skull and vertebral column was observed. However, the most marked adverse effect on the offspring was related to their fertility. In 97% of mice exposed prenatally to 40 or 160 mg/kg of benzo[a]pyrene, total sterility was observed. Among those exposed prenatally to 10 mg/kg, female offspring yielded significantly smaller and fewer litters and fertility was reduced by 50% in male offspring exposed in utero to this dose of benzo[a]pyrene. Histological examination revealed that many of the benzo[a]pyrene-exposed female offspring had hypoplastic ovaries with deficient follicular development or were completely lacking in ovaries. In the males, altered spermatogenesis and germ cell aplasia was observed, with a reduction in the size of the testes and seminiferous tubules and an increase in the amount of interstitial tissue.

Shum et al., (1979) studied the teratogenic and in utero toxic effects of benzo[a]pyrene exposure in mice. On days 7 or 10 of gestation, doses of between 50 and 300 mg/kg were given intraperitoneally. Two strains of mice were examined, one known to manifest much more inducibility of AHH than the other ("responsive" and "non-responsive" strains, respectively). (The criteria for designation of "responsiveness" are given in the text.) With the use of backcrosses, it was shown that among the progeny of "non-responsive" mothers, "responsiveness" in fetuses was associated with an excess of still-births, resorptions, congenital anomalies and covalent binding of benzo[a]pyrene

metabolites to fetal DNA and protein, as well as decreased weight relative to "non-responsive" fetuses from the same uterus. Among progeny of "responsive" mothers, differences in these variables were not found for "responsive" and "non-responsive" fetuses from the same uterus. The authors attributed the absence of effect in this situation to overriding of the influence of fetal genetic differences by the relatively high levels of benzo[a]pyrene metabolites originating from the mother. The types of malformations observed were mainly cleft lip and palate, hemangioma, and club foot.

Hoshino et al., (1981), utilizing the same general methods as Shum et al, confirmed the latters' findings of increased resorptions and reduced fetal weight; in terms of malformations, an increase was found only for cervical ribs occurring among fetuses of "responsive" mothers.

Legraverend et al., (1984) used a similar protocol, with the exception that benzo[a]pyrene (120 mg/kg per day) was administered orally between days 2 and 10 of gestation. It was found that among the progeny of "non-responsive" mice, an excess of interuterine toxicity and malformations occurred among "non-responsive" relative to "responsive" fetuses. This difference was not observed in the progeny of "responsive" mice. Pharmacokinetic studies and high-performance liquid chromatographic analysis of benzo[a]pyrene metabolism <u>in vitro</u>, carried out by the authors, were consistent with "first-pass elimination" kinetics. The interpretation was that, in the "non-responsive"

mother little induction of benzo[a]pyrene metabolism occurs leading to higher levels of placental transfer of benzo[a]pyrene. In the "responsive" mother, relatively enhanced benzo[a]pyrene metabolism occurs, leading to less access to embryos by benzo[a]-pyrene. The authors demonstrated the occurrence of more benzo-[a]pyrene metabolites among "non-responsive" than "responsive" embryos. These observations are the opposite of those reported by Shum et al., (1979) and indicate the potential importance of route of administration in instances when a teratogen leads to induction of its own metabolism.

The embryotoxicity and teratogenicity of benzo[a]pyrene in the rainbow trout were studied by Hannah et al., (1982). Benzo[a]pyrene-coated sand produced aqueous concentrations between 0.08 and 2.99 ppb, comparable to levels occurring in polluted rivers. Benzo[a]pyrene exposure was associated with an increased duration of the hatching process. In the experimental group, increased rates of morphological abnormalities were observed at aqueous concentrations of as low as 0.21 ppb. The anomalies included deficient yolk sacs, reduced body pigment, kyphosis, and eye abnormalities or agenesis.

The embryotoxic effects of benzo[a]pyrene were studied in Mallard ducks by Hoffman and Gay (1981). Petroleum hydrocarbon mixtures (described in detail in the text) were applied to the egg shell surface and the effects of adding three different concentrations of benzo[a]pyrene to this mixture (resulting in dosages of 0.02, 0.10 and 0.5%) were examined. Little effect on

survival was associated with exposure to the petroleum hydrocarbon mixture alone. The addition of benzo[a]pyrene at a concentration of 0.02% resulted in an increased rate of abnormalities among survivors and reduced embryonic growth. A large reduction in survival was associated with a benzo[a]pyrene concentration of 0.1% and a higher rate of abnormalities among survivors was observed than in the 0.02% group. 100% mortality occurred in the 0.5% benzo[a]pyrene group. Abnormalities included incomplete feather formation, anophthalmia, exencephaly, incomplete ossification, gastroschisis, bill defects and incomplete liver development.

In mouse blastocysts exposed in vitro, Iannacconi et al (1984) studied the reproductive toxicity associated with endometrial cell-mediated metabolism of benzo[a]pyrene. Mouse endometrial cells were demonstrated to have inducible AHH activity. Microsomes from induced endometrial cells showed a metabolic profile compatible with the capacity to produce benzo[a]pyrene 7,8-dihydrodiol 9,10-epoxides from benzo[a]pyrene or benzo[a]pyrene 7,8-dihydrodiol. Embryos obtained from pregnant mice on day 3 post-coitum were incubated with endometrial cell microsomes and benzo[a]pyrene-trans-7,8-dihydrodiol, at concentrations ranging from 0 to 1.0 um. Following the incubation, the embryos were transferred to pseudopregnant surrogate mothers which were sacrificed 7 days later. At the highest exposure concentration, a significant reduction in the proportion of mothers remaining pregnant was

observed. Decidual swelling volume and blastocyst implantation were reduced in a dose-dependent manner. Thus, benzo[a]pyrene metabolites formed in the presence of endometrial cell microsomes proved capable of disruption of normal blastocyst development.

5.2.8 Transplacental Carcinogenesis

The possible association of benzo[a]pyrene exposure with transplacental carcinogenesis has been studied by a number of investigators.

Bulay and Wattenberg (1970, 1971) injected mice intraperitoneally with 4 mg of benzo[a]pyrene on days 11, 13 and 15 of pregnancy. The possibility of post-natal benzo[a]pyrene exposure in milk was eliminated by the use of control dams to rear the pups. A highly increased rate of lung adenomas was observed in benzo[a]pyrene-exposed offspring.

Injection of this dose of benzo[a]pyrene in the last week of pregnancy has been reported to be associated with induction of tumours and hyperplasia upon culture of fetal mouse lung and kidney cells removed just before term (Shabad et al., 1972).

Barlow and Sullivan (1982) cited a Soviet investigator, Nikonova (1977), as having demonstrated increased susceptibility of offspring to tumour formation (relative to their mothers) following subcutaneous administration of benzo[a]pyrene to mice on day 18 and 19 of pregnancy.

Lasnitzki (1956) cultured explants of human fetal lung

tissue originating from therapeutic abortion material of 12 to 20 weeks gestation in the presence of 1 to 6 ug of benzo[a]-pyrene per ml of medium. Treatment-related hyperplasia of the bronchiolar epithelium was observed, with abnormal mitosis and irregular enlargement evident in newly-formed cells. At the highest dose level there was increased general proliferation with adenomatous features. It should, however, be borne in mind that the characteristics of cultured cells may differ from those developing in their natural habitat.

Urso and Gengozian (1984) have studied the relationship between immune response and benzo[a]pyrene-associated trans-placental carcinogenesis.

Benzo[a]pyrene (150 ug/g body weight) was administered to pregnant mice during days 11 to 17 of gestation. Relative to control animals exposed to corn oil alone, the offspring exposed to benzo[a]pyrene <u>in utero</u> manifested suppression of their capacity to produce antibody-forming cells against sheep red blood cells, to mount a mixed lymphocyte response, and to generate <u>in vivo</u> graft-versus- host responses. It was further observed that there was an 8- to 10-fold elevation in tumour incidence in the experimental group, relative to the controls. These results suggested that benzo[a]pyrene-associated immune suppression may be related to observed transplacental car-cinogenic effects.

5.3 Summary

The limited literature concerning the adverse reproductive effects of coal tar products and bitumens is indicative of the occurrence of a broad spectrum of such effects in the species studied. Further, the research concerning benzo[a]pyrene has been assessed from the perspective of reproductive toxicity - as a major representative of polycyclic aromatic hydrocarbon compounds, which are important constituents of coal tar products and related substances. No studies were found regarding human exposure, but the literature concerning other species is indicative of potential risks for most types of reproductive outcomes.

CHAPTER SIX

HUMAN CARCINOGENESIS

6.1 Case Reports

6.1.1 Coal Tar and Coal Tar Pitch

In the literature there are many case reports of cancer in humans related to coal tar and coal tar pitch exposures. These date back to Manouvriez (1876) when he reported three cases of scrotal cancer, one case of scrotal and nose cancer, and two other types of cancer in a tar distillery. Tillmanns (1880) reported one case of scrotal cancer in a worker exposed to brown coal tar for 21 years. Ball (1885) described a case of scrotal cancer in a worker exposed to naphtha, creosote oil and pitch for nine years and one case of skin cancer in a worker occupationally exposed for 15 years in a tar distillery.

In 1892 Butlin described 39 cases of scrotal cancer among chimney sweeps and workers exposed to tar pitch and asphalt. Liebe (1892) discussed two cases of scrotal cancer with 11 to 16 years exposure to tar. Oliver (1908) described 13 cases of multi-site skin cancer with wide variation in length of exposure to coal tar products and Schamberg (1910) mentioned five cases of skin cancer among workers in a tar paper saturation plant. O'Donovan (1920) described 16 cases of skin cancer, five of which

were scrotal cancer. Southam and Wilson (1922) reported 141 cases of scrotal cancer in workers exposed to types of coal tar products.

Kennaway (1925) referred to 274 skin cancers, 90 of which were scrotal cancer only. These workers were exposed to pitch, soot, tar and shale oil. Four skin cancer cases in workers employed at a briquette factory were reported by de Vries (1928). Other large-scale reports of skin cancers among coal tar workers are those of Heller (1930), who described 40 cases, and Henry and Irvine (1936), who referred to 132 cases of scrotal cancer. Henry (1937) described 1,487 scrotal cancers, and later in 1947, another 3,921 cases of skin cancer. Of the latter, 1,421 were scrotal cancer with exposure to substances all containing polycyclic aromatic hydrocarbons, and 2,500 other cases of skin cancer with similar type exposures. Dean (1948) described 27 cases of scrotal cancer with mixed exposure. This paper was followed by reports of Ross (1948); Cruickshank (1952); Patch (1954); Lenson (1956); Fife (1962); Spink (1964); Lee (1972); Durkin (1978); and Jarvis (1980). Recently, Millard (1986) described a case in which dozens of small papular basal cell carcinomas occurred in a worker exposed to coal tar.

6.1.2 Case Reports - Creosote

O'Donovan (1920) discussed 3 cases of skin cancer in men exposed occupationally to creosote. In one of these cases warts

had appeared on the hands, legs and behind the ears for 7 years after applying creosote to timber for 40 years. Cookson (1924) reported a metastasizing squamous epithelioma on the hand of a worker employed for 33 years in carrying creosote wood. The massive report of Henry (1947) contained a review of 3,753 cases of cutaneous epitheliomata. There was exposure to creosote in 35 cases or 39 body sites, 12 of which were of the scrotum. This large-scale report of 3,921 sites was reported to the British Medical Inspector of Factories covering the period of 1920 to 1945. Of these, 35 cases were exposed to creosote, and 14 or 15 sites occurred among workers treating timber with creosote. Nine or 11 cases occurred among people handling creosote in storage and 10 or 11 sites were reported among people using creosote as a releasing agent for brick molds.

For purposes of general comparison, the following incidence rates for Ontario residents of site-specific cancer are listed for the year 1982 for males.

Age Adjusted Incidence Rate for Males

All ages (1982)

per 100,000 (standardized to world population)

Number	Site	
162	Trachea, Bronchus and Lung	61.06
172	Malignant Melanoma of Skin	4.77
186	Testis	3.51
187	Penis and other male genital organs	1.04

No conclusion can be drawn about the relative health

experience of the exposed population compared to the general population from the cited case reports.

6.1.3 Case Reports - Bitumens

Oliver (1908) reported 2 cases of scrotal cancer in workers exposed to bitumens for 13 and 20 years respectively. In 1 case there was concomitant exposure to coal tars and pitches. Henry (1947) reviewed 3,753 cases of skin cancer in 2,975 persons. Of these cases, 13 were in 12 persons applying road surface material and 9 were in makers of road material. Most of these workers were also in contact with coal tars. A summary of some case reports of skin cancer in workers exposed to coal tars, pitch, creosote, and bitumens is tabulated in Table VI - 1.

Table VI - 1 Case Reports of Skin Cancer in Workers Exposed to Coal Tars, Pitch, Creosote, and Bitumens

Author/year	Occupation of Subjects and/or Exposure	Duration of Exposure	Site and No. of Cancer Cases	Date of Case Verification
Tillmans 1880	Brown coal tar and paraffin	21 years	Scrotum and arm	1877
Ball 1885	Tar workers, tar distillery workers	9 years	1 scrotum 1 head	1881
Butlin 1892	29 chimney sweeps 1 tar worker 1 pitch and asphalt worker 1 gasfitter 7 other	18 years	39 scrotum	Not given
Liebe 1892	Tar workers	11-16 years	2 scrotum	1892
Oliver 1908	3 coal grease 2 asphalt 1 chimney sweep Tar workers	Not given 13-20 years, >25 years Not given	3 hands and arms 3 scrotum 6 or 7 cases (site not given)	1905-1908
Schamberg 1910	Tar-paper saturation workers	13-55 years	4 hand and arm 1 scrotum and hand	1910
O'Donovan 1920	3 creosote, 1 tar 1 gas worker; 3 tar, 2 gas workers, 3 pitch 2 others, 1 creosote	 Unknown to 40 years	5 scrotum 11 other	1903-1919
Southam & Wilson 1922	69 mule-spinners, 22 tar and paraffin, 1 sweep, 49 others	Not given	141 scrotum	1902-1922
Kennaway 1925	16 soot, 32 pitch, 11 tar, 31 shale-oil; 78 pitch, 23 tar, 49 soot, 34 shale-oil	Not given	90 scrotum 184 other	1900-1921 1910-1923
de Vries 1928	Briquette factory workers	11-20 years	2 scrotum 1 face and hand 1 hand	1913-1927

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Heller 1930	1 gas works, 2 gas works pitch, 1 coke oven pitch; 11 gas works, 4 roofers, 2 tar distillation, 1 road worker, 13 gas works pitch, 3 coke-oven pitch, 2 lampblack	Not given Not given	4 scrotum 36 other	1920-1928
Henry & Irvine 1936	89 cotton mule-spinners, 16 ex-mule-spinners, 2 gas retortmen, 2 tar distillers, 2 chimney-sweeps, 21 other	10-50 years	132 scrotum	1837-1929
Henry 1937	345 cotton mule-spinners, 103 chimney sweeps, 1039 others	Not given	1487 scrotum	1911-1935
Henry 1947	141 pitch, 48 tar, 299 pitch and tar, 12 creosote oil, 899 mineral oil, 15 shale-oil, 7 other; 606 pitch, 66 tar, 1147 pitch and tar, 27 creosote oil, 5 anthracene, 594 mineral oil, 38 shale-oil, 17 other	Not given	1421 scrotum 2500 other	1920-1945
Dean 1948	5 petroleum refiners, 6 machinists, 1 roofer, 1 boiler and chimney cleaner, 14 other	10-40 years	27 scrotum	1926-1947
Ross 1948	Tar and pitch workers	6-months 43 years	4 scrotum 4 arm and hand 15 head and face	1952
Patch 1954	Pitch, bitumen, slate powder and asbestos	27 years	1 neck	1952

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Lenson 1956	Creosote Paints	3 years 41 years	1 face	1955
Fife 1962	2672 tar and pitch, 491 mineral oil (cotton industries), 96 mineral oil (other industries)	Not given	3259 skin (site not specified)	1944-1959
Spink et al. 1964	Pipe jointers using a 20% tar mixture	17-35 years	2 scrotum 1 other	1941-1959
Lee et al. 1972	40 mule-spinning only, 11 mule-spinning and others, 6 pitch, tar or its products, 11 oil, 21 others	1-9 years 3-47 years 6-55 years	103 scrotum	1962-1968
Durkin et al. 1978	Coal tar, ultraviolet light, steroids for psoriasis	20 years	1 back	1974
Jarvis 1980	Pitch worker	14 years	1 scrotum	Not given
Millard 1986	Light oils, benzol, tar acids	45 years	1 face	1985

6.2 Human Epidemiology

6.2.1 Human Epidemiology - Coal Tar and Pitches

Henry et al., (1931) made a detailed study of 11,429 deaths of men who died of cancer of the bladder and prostate according to the last recorded occupation as given on the death certificate. The data were derived from 13,965 cases that occurred in England and Wales from 1921 to 1928. Expected numbers of deaths were calculated from death rates for cancers of the bladder/prostate in 5 year age groups according to the census occupation tables and were applied to the population of workers in each 5-year age group. It was found that among 2,665 tar distilling workers, 4 deaths from bladder cancer were observed with 1.2 expected. One death from prostatic cancer with 1.2 expected was found. Among 1,811 patent-fuel workers 2 deaths from bladder cancer were observed with 0.5 expected. One death from prostatic cancer was found with 0.4 expected. The consistency of the finding of elevated standardized mortality ratios (SMRs) for bladder cancer in nine of eleven occupational groups with exposure to coal gas, tar and pitches deserves our attention. Nevertheless, the problem with this study is that even with deaths accumulated over an 18 year period, single categories of deaths were often so small that few deaths could have occurred from a specific cancer. Moreover, comparison is made between occupation stated on a death certificate and census data. The

accuracy of diagnosis on a death certificate could be questioned and no information is given on the duration or type of occupational exposure.

Henry (1946) calculated crude cumulative rates of scrotal cancer mortality. These cases of scrotal cancer deaths were reported to the Registrar General in England and Wales from 1911 to 1938. He classified 1,631 cases by occupation and divided them by the average population of the 1921 and 1931 censuses for each occupation. Detailed occupational populations were derived from the Board of Trade or a trade itself. The mortality rate for scrotal cancer for patent-fuel workers or pitch-briquette makers was 504 per million men based on 24 cases compared to a rate of 4.2 per million for the national average and rates of 1 per million or less for most other occupations including service transporting retail trades.

Doll et al. (1965) reported the results of an eight-year prospective mortality study of 11,499 gas workers and pensioners at four British gas companies starting from September, 1953. Occupational exposure to products of coal carbonization was classified as high, intermittent or low. Fifty of the subjects (0.4%) were not traced until the end of the study. Causes of death were identified from death certificates and were compared with mortality figures for all men in England and Wales during the same period.

Bronchitis and lung cancer mortality were highest in those most heavily exposed in the retort house and lowest in those with

minimal or no exposure. Lung cancer mortality and bronchitis mortality in the heavily exposed group were both higher than the regional rates. There were no differences in smoking habits between any groups of workers and no differences between the smoking habits of the workers and those of the national population. Therefore, smoking habits do not help to explain the different incidences of lung cancer and bronchitis in the three occupational exposure groups.

Doll et al. (1972) did a further four-year follow-up study from the same four gas companies studied earlier (1965). They added 4,687 workers from four additional area gas companies not previously studied. The employees were 40 to 65 years of age, all of whom had been employed for at least five years. Causes of death were ascertained from death certificates. Death rates were compared with age-adjusted rates for England and Wales.

Doll et al. (1972) concluded that exposure to the products of coal carbonization can lead to cancer of the lung, as suggested in their earlier finding (1965). However, the investigators were unable to explain why the mortality from lung cancer was higher in the intermittently-exposed workers than in the heavily-exposed workers in two of the four additional gas companies. Moreover, contrary to their earlier findings (1965), the additional data offered a very limited support to the view that bronchitis is a specific occupational hazard for gas workers. According to the authors, perhaps the large excess of deaths from bronchitis observed earlier among retort-house workers was

attributable to the poor working conditions during the war years.

Hammond et al., (1976) referred to a 12-year mortality study of 5,939 members of a roofers' union in the U.S.A., still alive in 1960. Only members with 9 or more years of union membership were included. Follow-up of the cohort through to 1971 was maintained for 5,788 members. Expected number of deaths was computed on the basis of United States life tables specific for age and single calendar year. It was found that the standardized mortality ratio (SMR) for all deaths was 103 in the first 6 years of the study and 110 in the second 6 years of the study. Lung cancer ratios generally increased with increase in time since joining the union. For the group with 9 to 19 years, 22 lung cancers were observed for an SMR of 92. For the group 20 to 29 years, 66 lung cancers were observed for an SMR of 152. For the groups 30 to 39 years, 21 cases were observed for an SMR of 150 and of the group with 40 plus years, 12 cases were observed for an SMR of 247. In the group with 20 or more years membership in the union it was found that the SMR for cancer of the oral cavity, larynx and esophagus was 195 with 31 observed cases. For cancer of the stomach, 24 cases were observed with an SMR of 167. For leukemia, 13 cases were observed for and SMR of 168. For cancer of the bladder, 13 were observed for an SMR of 168. Five deaths were from skin cancer other than melanoma for the total cohort with an expected number of 1.18. The major criticism of the study was that no data for smoking habits were given and such data were not taken into account in the analysis. Roofers

in the United States were mainly engaged in applying hot pitch or hot bitumen. In previous years coal tar pitch was used more frequently than petroleum pitch and there has been a significant recent trend towards the use of petroleum-based compounds. Specifically, with regard to this study, most of the men studied worked with both substances.

Menck and Henderson (1976) studied the occupational differences in lung cancer rates among white men in Los Angeles county. Mortality data for 1968 to 1970 and morbidity data from the County Cancer Registry for 1972 to 1973 were pooled. The 3,938 men included in the study were classified by their last recorded occupation in the industry in which they were employed. Data was obtained from death certificates for mortality in hospital records for incident cases. Age-adjusted expected numbers, deaths, and incident cases were calculated from the 1970 census records for Los Angeles county, classified by occupation and industry. A 2% sample of the total records was taken. A significantly increased risk of lung cancer was observed among roofers with a SMR of 496 based on 6 deaths and 5 incident cases. In this study, the subdivision of occupations or industries does not provide sufficient numbers or a precise classification of jobs to characterize different exposures. Moreover, there is a difference in the numerator and denominator of the ratio from the sources of information on occupation. Again smoking habits were not taken into account in the analysis.

Decoufle et al., (1977) used the records of Roswell Park

Memorial Hospital in New York in a review of cases of cancer compared with cases of non-neoplastic diseases during 1956 to 1965 in a survey of occupations. Clerical workers were used as a comparison group with other occupations. The relative risks were adjusted for age and smoking habits. It was found that among roofers a non-significant relative risk of 2.95 was reported for cancer of the buccal cavity and pharynx. The relative risk from lung cancer in this group was not commented upon.

Wang et al., (1983) discussed a Massachusetts mortality study which looked at optical lens workers exposed to pitch and abrasives while grinding and polishing lenses over the period 1956 to 1975. It was found that a statistically significant excess of cancers was observed with 70 observed and 48 expected. Expected deaths were computed from deaths among people in non-exposed occupations and from similar socio-economic strata. Excess rates of gastro-intestinal cancer were found with a mortality odds ratio of 2.2 for those with medium exposure and 2.5 for those with long-term exposure. However, it is difficult to evaluate in relation to pitch with the mixed exposure in this study.

McLaughlin et al., (1983) described a population-based case-control interview study of cancer of the renal pelvis. This was conducted in the area of Minneapolis-St. Paul. Seventy-four cases and 697 controls were included in the study. After adjustment for age and cigarette smoking, an elevated but not statistically significant odds ratio was found for

occupational exposures to petroleum or tar pitch. The odds ratio found was 2.4 with a 95% confidence interval of 0.9 to 6.1.

6.2.2 Human Epidemiology - Creosote

Henry (1946) calculated the crude mortality rates for scrotal cancer for groups occupationally exposed to creosote. It was found that the crude mortality rate for scrotal cancer during the period of 1911 to 1938 for brick makers exposed to creosote oil was 29 per million men based on 9 verified cases. This was compared to a rate of 4.2 per million for the national average and rates of 1 per million or less for groups not exposed to the suspected skin carcinogen. In addition there were several other creosote-exposed groups with increased rates based on fewer cases.

In 1983, Axelson and Kling reported on a cohort study of 123 Swedish workers who applied creosote to wood and who had exposure to creosote and arsenic between 1950 and 1980. It was found that 8 workers died from tumours whereas 6 were expected from rates derived from national statistics. In a group of 21 workers who had been exposed only to creosote for 5 years or more, 3 deaths from cancer including leukemia, pancreas and stomach were observed as compared to the expected value of 0.8. The levels of exposure were not reported.

6.2.3 Human Epidemiology - Coke Oven Emissions

Kuroda (1937) did the first epidemiological study of lung cancer related to occupation in the gas-generator plant of the coking operation of a steel company in Japan. This cross-sectional study of current workers identified 61 malignancies during the period 1931 - 1935, of which 12 developed in the lung. The most striking observation was that all lung cancers occurred in the gas-generator workers. These workers had been exposed in the gas-generating plant for an average of 15.6 years.

Reid and Buck (1956) studied the causes of death among current and retired workers at British coking plants during 1949-1954. The study population consisted of 8000 current workers, for whom information on age and job distribution was obtained from a special census taken in 1952. Complete job histories (nature and duration of different jobs held in the plants) were obtained on a 10% sample. The workers were classified into four main groups. The first group consisted of men involved in operating the coking ovens, filling the oven, etc. The second group consisted of men involved in the recovery of bi-products such as tar, ammonia, and benzol. The third group was composed of workers whose duties and contacts with the coking processes varied greatly. Maintenance men and craftsmen who occasionally were in contact with the processes fell into the last group. Mortality by cause and occupational exposure is summarized in Table VI - 2.

Table VI - 2. Mortality# in Coking Plant Workers According to Occupational Exposure*

	Mortality by last Job Held						Mortality by Work History					
	Oven Workers		Bi-products Workers		Maintenance Workers		Men Employed at Any Time as Oven Workers		Men Never Employed as Coke Oven Workers		Men Employed at Any Time as Bi-product Workers		Men Never Employed as Bi-product Workers	
	O	E	O	E	O	E	O	E	O	E	O	E	O	E
Respiratory Cancer	4	5	3	3	14	14	14	10	7	13	4	6	17	17
All Cancers##	24S	16	9	9	38	48	40P	32	31	41	16	18	55	55
Other causes	50	49	29	26	166	141	71	95	174	121	46	53	199	163
Total excluding respiratory cancer	74	65	38	35	204	189	111	127	205P	162	62	71	254	218

* Adapted from Reid and Buck 1956.

\# O = observed deaths, E = expected deaths (adjusted for age) based on an unspecified industry for the period 1949-1954.

= "All cancers" was probably meant to be reported by Reid and Buck as "all other cancers." Otherwise the number for the "total excluding respiratory cancer" is in error.

S = Significantly in excess of expected ($P < 0.05$, two-tailed test).

P = Significantly in excess of expected ($P < 0.05$, one-tailed test).

A total of 337 deaths occurred among current workers. Information was available on the deaths of 214 retired workers. For current workers during the study period, standardized mortality ratios (SMRs) were determined using a large industrial population' for comparison. The SMR for lung cancers for those currently employed was 80 and for all cancers was 150. For those who had ever' worked in coke ovens, based upon an estimate from a 10% sample, the SMR was 140 for lung cancer in coke-oven workers and 125 for all cancers. The incidence of lung cancers among all cancer deaths for retired workers was 30% compared to 25% for coke-oven workers. Therefore, the authors stated that there was no increase in risk of cancer associated with work at the coke ovens. However, the amount of confidence that can be placed in the validity of the results of this study is in doubt. The authors fail to define clearly the basic study population. Similarly, the number of workers falling into each of the four job groups was not given. The number of retired workers was not known, with the exception of the number of retirees who died. Since the ages of death of the retired workers were not known, mortality was not age-adjusted. Therefore, the proportional death rates in retired workers are difficult to evaluate. There was no follow-up after 1954, latent effects were not adequately considered. In short, this study leaves many unanswered questions and would seriously underestimate risks.

In 1969, Lloyd and Ciocco reported on a large occupational study of 59,072 steelworkers, including coke oven workers,

employed in 1953 at seven steel plants in the Pittsburgh area (Allegheny County, PA, USA). Records of the workers were collected between July, 1962, and December, 1964, at the personnel offices of the plants. Mortality was reported by age, race, and cause of death. For workers leaving employment before January 1, 1962, the follow-up schema was quite exhaustive (references to death lists and city directories, inquiries to local, state, and federal agencies etc.). It was found that the average annual crude mortality rates were lower among the steelworkers than among the male population of Allegheny county.

During the seventies, extensive epidemiologic studies of coke oven workers by Lloyd (1971), Redmond et al., (1972), Redmond et al., (1976), and Redmond et al., (1979) indicated that workers exposed to coke oven emissions were at an increased risk of (particularly lung) cancer and, possibly, from cancer of the genito-urinary system.

Lloyd (1971) did a detailed review of risk within the coke plant environment. A total of 3,530 coke plant workers employed in 1953, or in prior years, were included in the study: 2048 at the ovens and 1482 in non-oven areas. The workers were divided into occupational groups depending on their respective job locations, the expected level of exposure to coke oven effluents, and the length of employment at the coke ovens. The SMR for respiratory cancers among coke-oven workers was 248 (33 deaths) compared with an SMR of 47 (4 deaths) in non-oven workers employed in the coke plant, and most of the risk occurred in

non-white workers (Table VI - 3). A 5-fold risk of lung cancer was reported for men working on the tops of the coke ovens, and a 10-fold risk of lung cancer for men employed five or more years at full-time topside jobs (Table VI - 4 and Table VI - 5). The study also showed that there was a significant excess of intestinal cancer, excluding the rectum (SMR, 316), among coke-plant workers who had never worked at the ovens. Two kidney cancers occurred in those who had worked at any time topside on the ovens compared with 0.6 expected, and two lymphomas also occurred in the same group compared to 0.6 expected. The author has suggested that workers occupationally exposed to emissions from the high-temperature carbonization of coal have an excessive liability for lung cancer. One major flaw of this study is the fact that smoking, a potential confounding factor, was not adequately addressed. The possibility of a synergistic effect of smoking and coke emissions cannot be ignored.

Table VI - 3. Number Employed, Observed and Expected Respiratory Cancer Deaths, and Standardized Mortality Ratios (SMRs) of Coke Oven Workers Employed in Allegheny County, Pennsylvania in 1953 and Prior Years by Race*

	Coke Plant				Coke Oven				No-oven			
	Number Employed	Observed Respiratory Cancer Deaths	Expected Respiratory Cancer Deaths	SMR	Number Employed	Observed Respiratory Cancer Deaths	Expected Respiratory Cancer Deaths	SMR	Number Employed	Observed Respiratory Cancer Deaths	Expected Respiratory Cancer Deaths	SMR
Total	3530	37	21.8	170@	2048	33	13.3	248@	1482	4	8.5	47
White	2369	11	12.2	90	993	8	5.0	160	1376	3	7.3	41
Nonwhite	1161	26	9.6	271@	1055	25	8.4	298@	106	1	1.2	--@@

* Adapted from Lloyd 1971.

@ Significant at P <0.01.

@@ Less than five deaths in both observed and expected; SMR and statistical significance not calculated.

Table VI. 4. Number Employed, Observed and Expected Lung Cancer Deaths and Standardized Mortality Ratios (SMRs) of Men Employed at Coke Ovens in Allegheny County, Pennsylvania In 1953 and Prior Years by Length of Employment (as of January 1, 1953)+

	Number Employed	Observed Lung Cancer Deaths	Expected Lung Cancer Deaths	SMR
Less than 5 yrs	1144	4	4.7	---@
White	593	3	2.2	---@
Nonwhite	551	1	2.6	---@
5 or more yrs	904	27	7.6	355##
White	400	5	2.6	192
Nonwhite	504	22	5.1	431##

+ Adapted from Lloyd 1971.

@ Less than five deaths in both observed and expected; SMR and statistical significance not calculated.

Significant at P<0.01.

Table VI - 5. Number Employed, Observed and Expected Lung Cancer Deaths and Standardized Mortality Ratios (SMRs) of Men Employed at Coke Oven Subdivisions in Allegheny County, Pennsylvania for More than 5 Years (as of January 1, 1953) by Work Area and Race*

	Number	Observed	Expected	
SMR	Employed	Lung Cancer Deaths	Lung Cancer Deaths	
Side Oven Only	496	6	4.1	146
White	171	2	1.1	---#
Nonwhite	325	4	3.0	---#
Side and Topside (less than 5 years full-time topside)	276	6	2.1	286##
White	202	2	1.3	---#
Nonwhite	74	4	0.8	---#
Full-time Topside	132	15	1.5	1000##
White	27	1	0.2	---#
Nonwhite	105	14	1.3	107##

* Adapted from Lloyd 1971.

Less than five deaths in both observed and expected; SMR and statistical significance not calculated.

Significant at P<0.01.

Redmond et al., (1972) further expanded the investigation of coke-oven workers by including ten additional plants from various parts of the United States and Canada. The added coke-oven workers had worked between 1951 - 1955. The total populations of coke-oven workers (4661) and non-exposed workers (25,011) were followed through 1966 - about 13 years. A significant excess relative risk for lung, trachea, and bronchus cancer occurred in both white and non-white workers. In addition, a significant ($P<0.05$) excess in genitourinary cancer was found among non-white workers who had worked topside of the ovens throughout their work history (Table VI - 6). The authors also analyzed the combined effect of length of employment and work environment. Malignant neoplasms of the lung, trachea and bronchus were found to be elevated for all oven workers having worked 5 years or more. This excess was found to follow a dose-response relationship (Table VI - 7).

Table VI - 6. Number Employed, Observed and Expected Deaths, and Associated Relative Risks From Malignant Neoplasms of the Lung, Trachea, and Bronchus and The Genitourinary Organs for White and Nonwhite Coke Oven Workers Employed From 1951 to 1955 at Ten Non-Allegheny County Steel Plants and at Two Allegheny County, Pennsylvania Steel Plants*

Group at Risk	Number Employed	Deaths from Malignant Neoplasms of the Lung, Trachea, and Bronchus			Deaths from Malignant Neoplasms of the Genitourinary System		
		Observed	Expected	Relative Risk	Observed	Expected	Relative Risk
Non-Allegheny County							
White	1445	13	7.5	3.02#	2	1.8	---S
Nonwhite	1860	23	13.4	2.09##	10	5.7	3.02#
Total	3305	36	20.9	3.00##	12	7.5	2.42#
Allegheny County							
White	534	4	3.4	---S	5	0.9	6.99##
Nonwhite	822	29	17.3	3.77##	4	4.9	---S
Total	1356	33	20.7	2.69##	9	5.8	1.76
White	1979	17	10.8	2.06##	7	2.7	3.49##
Nonwhite	2682	52	30.7	3.35##	14	10.6	1.60
Total	4661	69	41.5	2.85##	21	13.3	2.05##

* Adapted from Redmond 1972.

\# Significant at P<0.05 as calculated by a summary chi-square statistic with one degree of freedom.

\#\# Significant at P<0.01 as calculated by a summary chi-square statistic with one degree of freedom.

S Less than five deaths in both observed and expected; relative risk and statistical significance not calculated.

Table VI - 7. Observed and Expected Deaths and Relative Risks for Neoplasms of the Lung, Trachea, and Bronchus and Kidney for Coke Oven Workers Employed from 1951 to 1955 at ten non-Allegheny County Steel Plants and for Coke Oven Workers Employed During 1953 at Two Allegheny County, Pennsylvania Steel Plants by Length of Employment*

Malignant Neoplasm	Total Oven (Number Employed=4661)			Five Years or More Coke Oven (Number Employed=1704)			Five Years or More Full-Time Topside (Number Employed=328)		
	Observed Deaths	Expected Deaths	Relative Risks	Observed Deaths	Expected Deaths	Relative Risks	Observed Deaths	Expected Deaths	Relative Risks
Lung, trachea, and bronchus	69	41.5	2.85##	55	28.0	3.48##	25	7.4	6.87##
Kidney	8	2.6	7.49##	5	1.6	5.69	0	0.1	---S

	Five Years or More Topside and Side Oven Exposure (Number Employed=243)			Five Years or More Side Oven, Never Topside (Number Employed=851)			Less Than Five Years Coke Oven (Number Employed=2957)		
Lung, trachea, and bronchus	15	5.5	3.22##	15	8.7	2.10#	14	9.9	1.70
Kidney	3	0.4	---S	2	0.7	---S	0	0.2	---S

* Adapted from Redmond et al. 1972.

\# Significant at P<0.05, significance based on a summary chi-square with one degree of freedom.

\#\# Significant at P<0.01, significance based on a summary chi-square with one degree of freedom.

S Less than five deaths in both observed and expected; relative risk and statistical significance not calculated .

The relative risk of kidney cancer was 7.49 (8/2.6; significant) in total oven workers. There was no elevated risk of bladder or skin cancer.

Mazumdar et al., (1975) based on the mortality data from the Lloyd and Redmond et al. studies, tested the levels of benzene-soluble particulates in ten coke-oven plants. The particulates were measured for the topside and side oven areas of the coke-oven to analyze cancer mortality dose-response among the workers. The exposure level of particulates for the workers was arrived at by multiplying the exposure for the area where the person worked (mg/m^3) times the length of the time in months that the person worked there. There was no association between mortality from lung cancer and dose in white workers (Table VI - 8). However, there were fewer white workers than non-white workers working at the topside of the coke ovens, which would have reduced the probability of detecting a cancer risk for whites in the high exposure group and of detecting a cancer mortality dose-response. No increased risk of lung cancer was seen for individuals exposed to $\leq$ 200 mg/- month benzene-soluble material. However, a diluting effect may result from inclusion in the study group of coke oven workers. As the authors themselves indicate the average latent period for occupational lung cancer may range from 15 to 25 years, the workers in this study were followed for a period of 14 years only.

A historical cohort study by Davies (1977) included all coke oven workers (610) from 1954 through 1965 and compared the

Table VI - 8. Age-adjusted Death Rates for Lung Cancer Based on Mortality Observed During 1951-66 For White and Nonwhite Coke Oven Workers by Cumulative Exposure*

	Cumulative Exposure (mg/m3 months)							
	<199		200-499		500-699		700+	
	Nonwhite	White	Nonwhite	White	Nonwhite	White	Nonwhite	White
Number at Risk	865	970	1042	807	422	140	353	62
Number of Deaths	2	6	13	8	13	3	24	0
Rate/10000	4.0	15.4	12.9	10.5	24.9	13.5	54.6	--

* Adapted from Mazumdar 1975.

Age-adjusted rate based on the age distribution of the nonwhite coke oven workers.

mortality experience with that of England and Wales. There was no excess of lung cancer but there was an elevated SMR for colorectal cancer (192; five deaths) and bladder and kidney cancers (252; three deaths); however, the numbers were small in this study. Moreover, there was a significantly reduced level of cardiovascular disease in the group, which may suggest a selection bias.

Redmond et al., (1976) did an update of the historical prospective cohort study begun by Lloyd. The findings confirmed a statistically significant excess of lung cancer in coke oven workers. Redmond et al., continued their earlier study (1972) on the excess of respiratory cancer. This time a longer period of follow-up and aging of the cohort made it possible to consider 10 + and 15 + years of exposure (Table VI - 9). A strong dose-response for cancer mortality of all sites was also found to be associated with the length of exposure and the work area (Table VI - 10).

Table VI - 9. Number Employed, Observed Deaths, and Relative Risks of Death from Cancers of the Respiratory System, 1953-1970, for Coke Oven Workers by Work Area and Length of Employment Through 1953*

Work Area	Years Employed Through 1953								
	5+			10+			15+		
	Number Employed	Observed Respiratory Cancer Deaths	R.R.###	Number Employed	Observed Respiratory Cancer Deaths	R.R	Number Employed	Observed Respiratory Cancer Deaths	R.R.
Coke Oven	993	54	3.02##	574	44	3.42##	325	33	4.14##
Oven Topside Full-Time	150	25	9.19##	72	16	11.79##	29	8	15.72##
Oven Topside Part-Time	290	12	2.29##	245	16	3.07##	159	18	4.72##
Oven Side Only	553	17	1.79#	257	12	1.99##	137	7	2.00

* Adapted from Redmond et al. 1976.

\# Significant at P<0.05.

Significant at P<0.01.

Relative risks compared to all other steelworkers.

Table VI - 10. Number Employed, Observed Deaths, and Relative Risks of Death from Malignant Neoplasms, 1953-1970, for Coke Plant Workers by Work Area and Length of Employment Through 1953 (adapted from Redmond et al. 1976)*

Work Area	Number Employed	Observed Respiratory Cancer Deaths	R.R.	Number Employed	Observed Respiratory Cancer Deaths	R.R.	Number Employed	Observed Respiratory Cancer Deaths	R.R.
Total Coke Plant	1860	166	1.47##	1194	136	1.50##	790	108	1.62##
Coke Oven	993	101	1.66##	574	85	1.95##	325	63	2.40##
Oven Topside Full-time	150	35	3.70##	72	22	5.12##	29	12	7.63##
Oven Topside Part-time	290	26	1.59#	245	31	1.85##	159	32	2.73##
Oven Side Only	553	40	1.17	257	32	1.46	137	19	1.51
Nonoven	836	65	1.28	578	48	1.10	392	39	1.13
No One Coke Plant Area	31	0	---S	42	3	---S	73	6	1,34

* Adapted from Redmond et al. 1976.

Significant at P<0.05.

Significant at P<0.01.

S Less than five deaths in both the observed and expected number of deaths; relative risk and statistical significance not calculated.

The most recent follow-up of the workers studied by Redmond et al., extending the observation period for mortality through 1975, were reported by Redmond et al. in 1979. Findings were consistent with earlier reports that there were significant excess risks of cancers of the lung and of the genito-urinary organs, especially kidney, among coke-oven workers. A summary of some of the coke oven mortality studies is shown in Table VI - 11.

Some investigations have monitored the urine mutagenicity of exposed workers as a marker of risk to human carcinogenesis. Kriebel et al., (1983) analyzed urine samples from 12 non-smoking coke-plant workers who worked on or along the coke batteries. There was a significantly higher mutagenic activity in Salmonella typhimurium strain TA1538 in the presence of a liver metabolic system than was in samples from a non-smoking group of 35 office and laboratory workers. No significant difference was found in studies using strain TA100.

Moller and Dybing (1980) tested the mutagenic activity of urine concentrates from coke plant workers in the salmonella/mammalian microsome assay. Urine was collected before and after work from 10 smoking workers (ten to 20 cigarettes/day) and from ten non-smoking workers. As shown below, only three job types were sampled: foremen, truck drivers, and coke oven battery workers.

Table VI - 11. Summary of Coke Oven Mortality Studies*

Author and Year of Report	Study Population	Comparison Group	End of Follow-up on Vital Status	Findings
Lloyd and Ciocco (1969)	Steelworkers at seven plants in Allegheny County, Pennsylvania employed in 1953	Allegheny County male population in 1953	December 31, 1961	Average annual crude mortality rates were lower among the steelworkers than among the male population of Allegheny County.
Lloyd et al. (1970)	Different job categories within the steelworker population employed at seven plants in Allegheny County, Pennsylvania in 1953	All steelworkers employed at seven steel plants in Allegheny County in 1953.	December 31, 1961	Nonwhite coke plant workers employed at least 5 years had significantly higher total mortality rate (96 observed, 78.7 expected, $P<0.05$), and a significantly ($P<0.05$) higher cancer mortality rate (40 observed, 19.6 expected, $P<0.01$); most of the excess cancer mortality was due to lung cancer mortality (25 observed, 7.3 expected).
Lloyd (1971)	Steelworkers employed in 1953 who worked or previously had worked in the coke plant at two Allegheny County, Pennsylvania steel plants	All steelworkers employed at seven steel plants in Allegheny County in 1953.	December 31, 1961	An increase in respiratory neoplasm deaths was found for all coke oven workers as well as a significant excess of mortality, all causes, for workers who had worked full-time top-side. The respiratory cancer excess was significant ($P<0.01$) only among nonwhite workers. A dose-response for respiratory cancer mortality was evident by work area for workers who had worked 5 or more years.
Redmond et al. (1972)	Coke oven workers employed at two Allegheny County, Pennsylvania steel plants in 1953	All men who never worked at the coke ovens at the respective Allegheny County steel plants	December 31, 1966	A significant excess in respiratory cancer deaths was found for the non-Allegheny County plants (33 observed, 20.7 expected, $P<0.01$); the Allegheny County plants continued to have a significant ($P<0.01$) excess of respiratory cancer deaths.
	Coke oven workers employed at 10 non-Allegheny County steel plants from 1951 to 1955	Nonoven workers employed at the respective non-Allegheny County steel plants from 1951 to 1955		Deaths from malignant neoplasms of the genitourinary system were found to be significantly in excess among non whites in the non-Allegheny County plants (10 observed, 5.7 expected, $P<0.05$) and significantly in excess among whites in the Allegheny County

Table VI - 11
cont'd...page 2

				plants (5 observed, 0.9 expected P<0.01). Lung cancer followed a dose-response by work area (top-side, part-time topside, or side oven only) for all workers who had worked 5 years or more at the coke ovens. For nonwhites at all plants lung cancer was found to follow a dose-response by length of time worked (< or > 5 years).
Mazumdar et al. (1975)	Coke oven workers employed at two Allegheny County, Pennsylvania steel plants in 1953.	All men who never worked at the coke ovens at the respective Allegheny County plants	December 31, 1966	A considerable difference in exposure to coal tar pitch volatiles was found for different work areas. The level of exposure and length of time exposed were both found to be related to the development of cancer, particularly lung cancer.
	Coke oven workers employed at 10 non-Allegheny County steel plants from 1951 to 1955	Non oven workers employed at the respective non-Allegheny County steel plants from 1951 to 1955		
Redmond et al. (1976)	Steelworkers employed at seven Allegheny County, Pennsylvania steel plants in 1953 who worked in the coke plant prior to or during 1953.	All steelworkers employed at the seven Allegheny County, Pennsylvania steel plants in 1953	December 31, 1970	The statistically significant excess of respiratory cancer mortality and cancer mortality, all sites, continued. Length of exposure was divided into 5+, 10+, and 15+ years. A clear dose-response was evident both by length of exposure and by work site.
Redmond et al. (1981)	Steelworkers employed at seven Allegheny County, Pennsylvania steel plants in 1953 who worked in the coke plant prior to or during 1953	All steelworkers employed at the seven Allegheny County steel plants in 1953	December 31, 1975	For the two largest Allegheny County coke plants, the excess risks for workers employed at the coke ovens for five or more years for lung cancer and kidney cancer were 2.63 (63/28.3) and 3.55 (6/1.8), respectively. Excesses of deaths from cancers of the large intestine and pancreas were seen in white workers only in coal-handling

Table VI - 11
cont'd...page 3

	Coke oven workers employed at 10 non-Allegheny County steel plants from 1951 to 1955.	Non-coke oven workers employed at the respective non-Allegheny County steel plants from 1951 to 1955.	and all other non-oven areas. The relative risks being 2.11 (P<0.05) and 2.44 (P<0.05).

* Adapted from EPA 1984.

Job Types	Number of Smokers	Nonsmokers
Coke oven battery workers	5	2
Truck drivers	4	6
Shift foremen	1	2

Within the job type "coke oven battery workers" includes larry car operators, door cleaners, etc., who would have a higher exposure to coke oven emissions than would the other two job types, "truck drivers" and "shift foremen". Ten non-plant smoking workers and four non-plant non-smoking workers were selected as controls. The mutagenic activity of urine samples from exposed workers showed no significant difference from those of non-exposed workers. The mutagenic activity of urine samples from smokers was significantly higher than that from non-smokers; however, it is difficult to interpret these results because of several deficiencies in the study design. Firstly, individual revertant counts (data are illustrated in histogram) and positive control data are not given. Secondly, it is not apparent whether the authors tested one concentration of urine or a range of concentrations. Thirdly, the authors employed the student's t-test to compare the exposed group to the non-exposed group; however, no comparison was made between individuals of a certain job type (i.e., exposure level) to the control population. Fourthly, jobs of the non-exposed workers were not specified. Lastly, the sample is too small, only 2 non-smoking workers with high coke oven emission exposure (coke oven battery workers) are included in the study.

Thus, despite some of the methodological shortcomings of the descriptive epidemiological studies outlined in this section, there is substantial epidemiological evidence to show that occupational exposure to coke oven emissions gives rise to an excess risk of death from lung cancer and cancers of the genito-urinary organs.

6.2.4 Human Epidemiology - Asphalt and Petroleum Pitch

Baylor and Weaver (1968), in a study of workers with at least 5 years and an average of 15.1 years of exposure to asphalt in 25 oil refineries, found a few cases of bronchitis, asthma and emphysema but no other significant health problems compared to a control population. Also included in their report were descriptions of the health status of workers involved in highway construction, roofing manufacturing and truck driving over asphalt highways. They concluded that exposure to petroleum asphalt constituted no health hazard.

Hammond et al., (1976) found an increased mortality from cancer and pulmonary diseases including emphysema, chronic bronchitis and asthma in a mortality study of roofers. As described earlier, there was a mixed exposure to asphalt and coal tar pitch fumes which resulted in increased rates of leukemia and cancer of the lung, upper respiratory tract, stomach, bladder, and skin. The independent effects of petroleum and coal tar-based products could not be differentiated and

smoking habits of the cohort were not considered.

Wilson (1984) reported a cluster of cases of malignant tumours in and near a village in Denmark. This case series of microscopically verified cancer cases was related to environmental and occupational exposures from an asphalt factory established in 1953. This descriptive report draws attention to the need for further epidemiological studies.

6.3 Summary

The purpose of this section is to summarize and assess the exposure and effect relationships of the substances under consideration. All epidemiological studies cited were examined for their methodological soundness and ability to demonstrate a reliable dose-response relationship. Only one study, that of Hammond (1976), was useful in examining the human carcinogenic doseresponse relationship of the coal tar and bitumen products. The main difficulty with this study was the lack of consideration of the effect of smoking. This may bias the estimation of dose-response effect to a significant degree. The interaction between previous exposure to coal tar pitch and recent exposure to asphalt because of the adoption of petroleum-based products severely confounds the consideration of an independent effect of the individual classes of substances.

As mentioned earlier in the animal carcinogenesis of creosote section, creosote and many of its component chemicals

have been demonstrated to cause cancer in laboratory animals (See Table IV - 3). Moreover, some of the case reports also suggested that creosote is a human carcinogen. However, there is no definitive data on the identity of the airborne component chemicals of creosote to which workers are exposed in wood treatment plants where creosote is used (EPA, 1982). In addition, there is no quantitative data on dermal exposure to these workers. This lack of information prevented the U.S. Environmental Protection Agency from conducting a quantitative assessment of risk of carcinogenicity in humans. Therefore, additional well conducted epidemiological studies of creosote plant workers and more extensive exposure studies are needed before one can quantitatively assess the potential human oncogenic risk from creosote exposure. Although no well designed epidemiological studies of workers mainly handling creosote have been carried out, the evidence of human cancer with exposure to creosote has been reconsidered and further supported by a review of polynuclear aromatic hydrocarbons (IARC, 1983).

Considering the numerous descriptive epidemiologic reports and extensive animal data, it is concluded that there is sufficient evidence in the literature concerning the carcinogenic potential of coal tar products in humans. (See Appendix II) The methodological shortcomings of the epidemiological reports, however, do not permit a valid estimation of dose-response effects. It is important to note that the cancer mortality studies carried out on coke oven workers by Lloyd, Redmond and

co-workers (Lloyd and Chiocco 1969, Lloyd et al., 1970, Lloyd 1971, Redmond et al., 1972, Redmond et al., 1976, Mazumdar et al., 1975, Redmond et al., 1979 and Sakabe et al., 1975) can only be used for comparative purposes. The general nature of these studies drawn from the steel industry cannot be extrapolated directly to those industries where exposures to coal tar products and bitumens may occur.

A mortality analysis of many occupations indicated an increased risk of mortality from scrotal cancer for creosote-exposed brickmakers. Malignant epitheliomas, about a third of which were of the scrotum, have been reported in several case reports of workers exposed to creosote. However, the only available cohort study, carried out by Axelson and Kling (1983), suffered from limitations of sample size. There is limited evidence that coal tar-derived creosotes are carcinogenic in humans. Nevertheless, taken together, the data show that coal tars and coal tar pitches are causally associated with cancer in humans and that creosotes derived from coal-tars are probably carcinogenic in humans (IARC 1985).

No human data about exposure solely to bitumens is available. A cohort study of US roofers (Hammond et al. 1976) indicates an increased risk for cancer of the lung and suggests increased risks for cancers of the oral cavity, larynx, oesophagus, stomach, skin and bladder and for leukemia. Nevertheless, as roofers may be exposed not only to bitumens but also to coal tar pitches and other materials, the excess cancer risk

cannot be attributed exclusively to bitumens. However, several case reports of skin cancer among workers exposed to bitumens are available (Oliver 1908, Henry 1947); exposure to coal-tars or products derived from them cannot be ruled out.

The application of this epidemiological evidence to the process of recommending an exposure standard is continued in the following chapter. Well designed epidemiological studies are urgently required to reduce the uncertainty surrounding the dose-response relationships of the complex mixtures under consideration.

CHAPTER SEVEN

RECOMMENDATION FOR A STANDARD

7.1 Introduction

This report has comprehensively reviewed the necessary scientific evidence relating to the health effects of exposure to coal tar, coal tar pitch, creosote, petroleum pitch, bitumen and asphalt, six substances which contain polynuclear aromatic hydrocarbons, (PAH's). The published literature has been critically appraised in terms of quality of evidence and interpretation.

Chapter I contains an introduction and definition of terms. The six above-mentioned substances are briefly described and placed in historical perspective.

Chapter II focuses on the pharmacokinetics of polynuclear aromatic hydrocarbons. The major routes of polycyclic aromatic hydrocarbon absorption are through inhalation and cutaneous exposure. Once absorbed they are distributed throughout the body via the circulatory system. Metabolic studies using benzo[a]pyrene as a model for PAH metabolism demonstrate that PAH's are metabolized and biotransformed through the cytochrome P-450 system. The removal of PAHs from the body occurs mainly through the liver, biliary tract and the elimination of feces.

Chapter III summarizes a number of experimental studies on the acute and chronic effects of exposure to coal tar products.

asphalt and bitumens both in humans and in animals. Most of these studies report apparent acute effects of these complex mixtures primarily on the skin and eyes. The literature is flooded with old and recent reports of photo-toxic skin reactions and several ocular manifestations ranging from marked photophobia to severe kerato conjunctivitis. In some of the studies, health problems such as nasal congestion, hoarseness, throat irritation, coughing, nose and throat inflammation and congestion due to exposure to coal tar pitch dusts are also described. All these effects require immediate attention considering the health effects of workplace exposures, and they necessitate preventive measures.

Chapter IV reviews a substantial number of studies of animal carcinogenesis associated with exposure to coal tar and petroleum products and coke oven emissions. Coal tar, coal tar pitch, creosote, coke oven emissions and asphalt exposure can result in the formation of skin tumours and/or lung tumours in animals. Reports in the experimental animal carcinogenesis studies of creosote and asphalt are more conflicting. Some of the studies in this category contained substantial methodological limitations, including a lack of specification of test groups, (e.g., age, sex, and strain), relatively small test groups, the absence of a concurrent control group, the omission of the dose administered, and the absence of survival data. In Section 4.2, mutagenicity studies of coal tar, coal tar pitch, creosote, coke oven emissions, and asphalt are considered. Most of these

studies report that the compounds were mutagenic.

Chapter V is an exhaustive review of the literature pertaining to the adverse effects of benzo[a]pyrene exposure on reproduction in animals. Metabolic considerations, mutagenicity, effects on estrous cycle, uterus and ovary, testicular effects, effects on fertility, transfer across placenta and mammary gland, embryotoxicity, fetotoxicity, teratogenicity and carcinogenesis are discussed in separate sections of the chapter. The evidence in the literature in regard to the adverse reproductive effects of coal tar and related exposures, though limited, suggests potential risks for most types of reproductive outcomes. There have been no studies involving human exposure.

Chapter VI is a compilation of case report studies of human carcinogenesis related to coal tar and petroleum products exposure. Some of the early case reports, summarized in 6.1, which date back to the early 19th century report finding skin and scrotal cancers. Section 6.2 summarizes epidemiologic studies of cancer in human populations and the relation of such cancers to environmental and occupational exposures to coal tar products, petroleum products, and other factors.

One of the most common difficulties encountered in the conduct and interpretation of epidemiologic studies is the control of confounding factors, especially cigarette smoking, which limit the usefulness of the studies in assessing the carcinogenic dose-response relationship of the substances under consideration, as outlined in Section 6.3. Nevertheless, there

is sufficient evidence concerning the human carcinogenic potential of coal tar products, specifically coal tar and coal tar pitch, in the literature to warrant stringent control of workplace exposures.

The evidence for the human carcinogenicity of creosote is limited due to the relatively few studies published to date and to inherent methodological limitations, such as insufficient sample size and latency effects. Adequate studies of the human carcinogenicity of asphalt have simply not been carried out and therefore no definitive conclusion can be drawn at this time on the relationship between human cancer and exposure to asphalt based on human epidemiological data. In the absence of adequate data on humans, it is reasonable for the purposes of standard setting to regard complex mixtures, for which there is sufficient evidence of carcinogenicity in animals, as presenting a carcinogenic risk to humans. On this basis, creosote and asphalt are included in this recommendation for an exposure standard for the practical consideration of the primary prevention of occupational cancers, and not for the purpose of scientific divertissement.

7.2 Approaches to Risk Analysis

This section deals with the estimation of risk associated with exposures to coal tar products, asphalt and petroleum pitch. In estimating such risks a number of approaches can be taken to account for the multiple health effects which can occur as a

result of exposure to the substances under consideration in this document.

One approach would consider a zero acute health effect exposure level based on reports of adverse health outcomes in the scientific literature reviewed in Chapter III. The advantage of this approach is that acute effects of these exposures are considered in a primary fashion and do not necessarily rely on often speculative risk projections for human carcinogenesis based on lifetime exposure. A clear disadvantage of this approach, however, is that risks from chronic health effects such as cancer may be ignored in the final risk assessment and reproductive hazards reviewed in Chapter V cannot be addressed.

A second approach would be to give a risk estimate based on dose-response data concerning chronic health effects, such as human cancer, which may have a long latency period between the time of first exposure and diagnosis of cancer. The disadvantage of this approach is the lack of sound long-term prospective mortality and morbidity studies on occupational groups which have well quantified exposures. In instances where this latter type of evidence does exist, the uncertainty of extrapolation to low dose level still remains in the establishment of a standard.

From the literature reviewed in Chapter VI, it is clear that descriptive and analytic epidemiology coupled with extensive experimental animal data support the association between exposure to complex mixtures containing polycyclic aromatic compounds and multi-site cancer. In order to estimate the specific or com-

parative risk of the various mixtures, it is assumed that unless evidence exists to the contrary, a carcinogenic response occurs at the dose levels used in the particular studies and that responses will occur at all lower doses with an incidence determined by the extrapolation model. Unfortunately very low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies and hence there is no solid scientific basis for any mathematical extrapolation model that relates carcinogenic exposure to cancer risk at extremely low concentrations.

A third approach would be to attempt to extrapolate toxicological data relating to animal carcinogenesis to humans. Garattini (1985) has analyzed the major components which make it extremely difficult to extrapolate toxicological data obtained with chemicals from animals to man. A first problem concerns the use of doses to express the unit of comparison across animal species; the dose is a parameter exogenous to the body and when a chemical enters the body concentrations should be utilized. There is in fact evidence that for several chemicals equal doses in different animal species do not mean equal concentrations in blood or tissues. For extrapolation purposes concentrations of chemicals should be measured as near as possible to the site of the toxic effect.

A second problem is the fact that several chemicals are transformed in the body into other chemical species - sometimes few and sometimes many - and some of these species (active

metabolites) display biological activity in some cases higher than, different from, or antagonistic to those of the parent compounds. Some of these metabolites are highly reactive and therefore bind to body components, particularly macromolecules such as proteins and nucleic acids. There is evidence that metabolism is quantitatively and/or qualitatively different in various animal species.

A third problem concerns the difference in various animal species, in the biological substrates on which chemicals exert their toxic effects. Equal concentrations of chemicals and their metabolites do not necessarily mean equal toxic effects across animal species because endogenous metabolic processes, cell permeability, enzymes, and receptors are not necessarily the same across animal species, including man.

A fourth approach utilizes the principle of ALARA which states that workplace exposures should be "As Low As Reasonably Achievable" and accepts that there exists an "acceptable risk" to which workers can be exposed. Two main difficulties are embodied in this approach excluding judgements about economic, ethical and social factors. Technical judgements of what is reasonably achievable in terms of measurement and control of a human carcinogen are problematic. In Section 7.5, which reviews the issues of exposure quantification, the applicability of the ALARA principle is expanded further.

Table VII - 1 Approaches to Risk Analysis

1.	Zero acute health effects
2.	Epidemiological Dose-Response Models
3.	Extrapolation from animals to man
4.	ALARA Principle

7.3 Assessment of Carcinogen Risk in Man

An understanding of biological mechanisms of carcinogenesis guides the type of risk model to use. It is assumed that a linear non-threshold model is the most viable model for any carcinogen and should be used as the primary basis for risk extrapolation to low levels of exposure to complex mixtures of PAH's. The extensive review of the literature does not indicate any direct evidence to the contrary. Richard Peto (1982) discussed the theoretical considerations of the carcinogenic effects of chronic exposure to very low levels of toxic substances and the related regulatory implications. He argues that if the dose-response relationship is found to be roughly a straight line, as for example is demonstrated in the coke oven emissions and lung cancer in humans data, then the graph of attributable risk against dose rate will go straight through zero, with a slope approximately equal to the slope seen in the observable range. Confidence limits in the observable range will be approximately equal to the confidence limits on the risk at low doses. They will differ from each other by less than a

factor of 2, and the risk at low doses is therefore sufficiently accurate to assist in the standard setting process.

A number of important assumptions in selecting the form of a model must be taken into consideration.

1. The model should conform to the observed data set.
2. The model should be based upon an acceptable biological theory that is consistent with known facts.
3. The model should be as simple as possible.

As mentioned in section 6.3, there does not exist an acceptable epidemiological data set, other than the coke oven emission studies, on which to base a valid and reliable risk-assessment model. Analysis of the coke oven studies has been carried out by Land (1976) who sorted the data assembled by Mazumdar et al. (1975) into 12 age groups and constructed specific exposure categories. Unfortunately this data, which has been considered by the Carcinogen Assessment Group of the Environmental Protection Agency (1984), cannot be extrapolated directly to the substances under consideration in this document due to differences in industrial processes and routes of exposure. The data can be used, however, for purposes of comparative risk analysis.

Lewtas et al., (1985) have described a comparative potency method for a comparative cancer risk assessment which is based on the hypothesis that there is a constant relative potency between two different carcinogens across different bioassay systems including animals and humans. The underlying assumption of this

comparative potency method is that the relative potency of two carcinogens in an *in vivo* or *in vitro* bioassay is directly proportional to the relative potency in humans. This assumption has been examined for three complex organic emission products from coke ovens, roofing tar, and cigarettes which are known to be human lung carcinogens (Table VII-2). For these three samples, the mouse skin tumor initiation relative potencies are within a factor of two, directly proportional to the relative potency estimated for these emissions from human lung cancer epidemiological data. The relative potencies, from the *in vitro* bioassays as compared to the human data, were similar for coke oven and roofing tar, but for the cigarette smoke condensate the *in vitro* tests predicted a higher relative potency.

The constant relative potency model does not assume that the carcinogens being compared are chemically related. Future evaluation of this model may show that it is only valid for either very similar chemicals or for combustion emissions where the carcinogens present in these mixtures are identical and vary only in their concentration. Upon chemical fractionation, however, significant differences were observed in the distribution of mutagenic activity in various fractions indicating that although these compounds may generally be polycyclic aromatic compounds, the specific mutagenic chemicals are different (e.g., by substitution of nitro, amino, or oxygenated moieties) as in the case for petroleum-derived products.

Barr (1985) critically reviewed methods of estimating

Table VII - 2. Comparative Mutagenicity and Carcinogenicity of Extractable Organics

Source a	Human Epidemiologic Data: Lung Cancer Unit Risks b	Bioassay Data: Animal in vivo: Mouse Skin Tumor Initiation c	Bioassay Data: Animal in vivo: Enhancement of Viral Transformation d	Bioassay Data: Short-Term in vitro: Mutation in L5178Y Mouse Lymphoma Cells e (-MA)	Mutation in L5178Y Mouse Lymphoma Cells e (+MA)	SCE in CHO Cells f (-MA)	SCE in CHO Cells f (+MA)	Ames Salmonella typhimurium TA98 g (-MA)	Ames Salmonella typhimurium TA98 g (+MA)
Comparative Emissions Human Carcinogens									
- Coke Oven Main	--	3.2	--	0.38	27.0	0.20	0.19	0.11	6.7
- Coke Oven Topside	9.3x10-4	2.1	1.2	0.71	12.0	0.41	0.03	0.7	1.1
- Roofing Tar	3.6x10-4	0.41	0.87	0.39	17.0	0.12	0.02	Neg h	0.86
- Cigarette Smoke Condensate	2.2x10-6	0.0024	0.35	0.39	0.79	0.12	0.08	Neg	0.57

* From Lewtas et al. (1985)

a References to the collection method and original bioassay dose-response data are indicated with each emission source.

b Lifetime risk/ug organics/m3 calculated from the linear nonthreshold extrapolation model (Thorslund, T.W.).

c Papillomas/mouse/mg based on papilloma multiplicity data in Sencar mice (Nesnow, S., Triplett, L.L., and Slaga, T.J.).

d Transformation frequency (transformed foci/10^6 surviving cells)/ug/ml.

f SCE/cell/ug/ml, (-MA) was a 21.5 h exposure and (+MA)was a 2 hr exposure.

g Revertants/ug (from simple linear regression analysis).

h Neg = Negative

carcinogenic potency for regulatory purposes and concluded that none of the methods, including epidemiology, bioassays, animal skin painting, in-vitro data, acute toxicity and structure activity relationships, are adequate for regulatory decision making when used alone. An approach that considers each of these methods as a contribution to the whole risk assessment process is currently viable, but clearly further development and refinement of these methods, where appropriate to human risk, is urgently required.

7.4 Biological Monitoring of Human Populations at Risk

Another epidemiologic approach utilizing new methods to monitor human populations exposed to carcinogens and pioneered by Perera et al., (1982, 1985), holds promise as a new way of detecting and quantifying carcinogenic risk to humans from complex mixtures of PAH's. This approach relies specifically upon methods to detect carcinogen-DNA adducts. The particular work they have described has been carried out as a prototype pilot investigation on populations exposed to benzo[a]pyrene .

Stowers and Anderson (1985) have described the in vivo formation of BP metabolite - DNA adducts characterized in a variety of target and nontarget tissues of mice and rabbits. Tissues included were lung, liver, forestomach, colon, kidney, muscle, and brain. The major adduct identified in each tissue was the (+)-7B,8a-dihydroxy-9a, 10a-epoxy-7,8,9,10-tetrahydro-BP

(BPDEI)deoxyguanosine adduct. A (-)-BPDEI-deoxyguanosine adduct, and an unidentified adduct were also observed. These and previous results strongly suggest that DNA in many human tissues is continuously damaged from exposure to BP and other PAH's. Moreover, DNA adducts formed from BP are persistent in lung and brain. Even if environmental exposure to PAH is too low to induce neoplasia, the accumulation of DNA adducts may produce aberrations in the transcripts of genetic information in various cells and lead to other toxic effects. Thus, further elucidation of the mechanism by which BP(PAH) metabolites bind to DNA of specific cell types, and of the cell-selective repair of the adducts, should enhance our understanding of the potential health risk from exposure to such environmental pollutants as PAHs.

The validation of these methods to definitively act as indicators of biologically effective dose and indicators of risk remains to be done. An epidemiologic study design utilizing a nested case-control study within a longitudinal prospective study offers tremendous potential to further clarify dose-response relationships with respect to carcinogenic potential.

Jongeneelen et al., (1985a) has described a method for isolating 1-hydroxypyrene from urine. The presence of 1-hydroxypyrene in urine was identified by fluorescence excitation and emission scanning after HPLC-separation. 1-Hydroxypyrene could be detected in the urine of rats following oral administration of as little as 0.5 ug pyrene. The dose-dependence of 1-hydroxypyrene in urine was evident after a wide range of pyrene dosing. After

therapeutic coal tar treatment of dermatological patients the enhanced excretion of 1-hydroxypyrene was highly significant. Employees of a creosote impregnating plant showed an excretion pattern of 1-hydroxypyrene which could be related to their work. 1-Hydroxypyrene in urine of non-exposed people was very low, but detectable. It is suggested that the method reported is suitable for the assessment of dermal uptake of pyrene, a compound that is commonly present in work environments which are associated with polycyclic aromatic hydrocarbons pollution.

The determination of mutagenic metabolites in urine with the aid of the Ames-assay was proposed to detect occupational exposure to mutagenic PAH. Kriebel et al., (1983) reported a higher mutagenic activity in the urine of non-smoking, coke plant workers than in the non-smoking control group. Several other reports have failed to detect enhanced excretion of mutagens in the urine of workers exposed to PAH (Moller and Dybing 1980; Clonfero et al. 1983; Bos et al. 1984b). However, a dose-dependent excretion of mutagens in the urine of rats after exposure to benzo[a]pyrene has been shown (Jongeneelen et al., 1985b). The poor sensitivity of the urinary mutagenicity assay to detect exposure to PAH seems to be the cause of negative results in human urine and the available data provide no evidence that pyrene itself is carcinogenic to experimental animals (IARC 1983).

Nebert and Jensen (1979) concluded that AHH inducibility or specific activity in cultured mitogen-activated lymphocytes or

any other similar test system is not a reliable enough test to be used as a biochemical marker for determining who is at risk for bronchogenic carcinoma or other cancers.

The ideal assay requirements for monitoring human carcinogen exposure are that the test is:

i) Sensitive

ii) Specific

iii) Quantitative

iv) Cheap

v) Rapid

vi) Reproducible

vii) Non-invasive.

Table VII - 3 summarizes currently available blood monitoring methods and their ability to fulfill ideal assay requirements:

Table VII - 3 Summary table of diverse blood monitoring methods and their ability to fulfill 'ideal' assay requirements*

	CA	SCE	MUT	UDS	Hb	Pr	PCM	PLL
Sensitive	-	-	?	-	+	+	+	+
Specific	-	-	-	-	+	+	+	-
Quantitative	+?	+?	+	-	+	+	+	+
Cheap	-	-	-	-	-	-	-	+
Rapid	-	-	-	+	-	-	-	+
Reproducible	+	+	?	+	+	+	+	+
Non-invasive	+	+	+	+	+	+	+	+

* From Garner (1985)

CA = Chromosome aberrations; SCE = sister chromatid exchanges; MUT = lymphocyte mutation; UDS = unscheduled DNA synthesis; Hb = hemoglobin alkylation; Pr = plasma protein binding; PCM = physico-chemical methods; PLL = post-labelling techniques.

These methods hold much promise for the future, however, at present, they are at the research and evaluation stage and are therefore limited in their usefulness for regulatory purposes.

7.5 Consideration of Exposure Quantification

When considering a workplace standard, careful review of environmental data of the substances of concern, as they occur in the general community, is important for comparison purposes. The most comprehensive environmental information is available on benzo[a]pyrene. There is a strong urban/rural gradient with concentrations higher in the cities than in the countryside. Concentrations are also very much higher in cities during the winter than in the summer months. A valuable summary of typical values of aerosol concentration for different geographic areas (annual averages) is presented in Table VII - 4.

Linstedt and Sollenberg (1982) reviewed benzo[a]pyrene exposure levels for different workplace categories and listed them according to the degree of exposure. Since most investigations have concerned BaP only, the classification was based on BaP analyses. Other analyses, e.g., CTPV, would very likely indicate a similar hierarchy.

1. <u>Very high BaP exposure</u> (>10 ug/m^3)

   Gas and coke works (topside work)

   Aluminum works (some jobs, eg, pin setters, potmen, cranemen)

Manufacturing of carbon electrodes (pitch bin workers)

Handling of molten tar or pitch (roofing, paving, insulation coating)

Chimney sweeping (from top)

Asphalting, if asphalt is mixed with coal tar

2. Fairly high BaP exposure (1 - 10 ug/m^3)

Gas and coke works in general (nontop-side work)

Blast furnaces

Steel works (some jobs)

Manufacturing of carbon electrodes (in general)

Aluminum works (in general)

Asphalting if asphalt is mixed with coal tar (in general)

3. Moderate BaP exposure (0.1-1 ug/m^3)

Steel works (in general)

Foundries (some jobs)

Welding of rails on track

Manufacturing of Soderberg electrode paste

4. Low BaP exposure (0.01 - 0.1 ug/m^3)

Automobile repair shops

Asphalt manufacturing (from petroleum)

Foundries (in general)

Construction of tunnels and rock chambers

Aluminum electrolysis halls with pre-baked electrodes

5. Very low BaP exposures (<0.01 ug/m^3)

Iron mines

Garages

Table VII - 4

Typical Values of Aerosol Concentration for Different Geographic Areas (Annual Averages)

Location	N. particles/cm^3	Mass Concentration ug/m^3	Benzene-Soluble Fraction of ug/m^3	Benzo[a]pyrene Fraction of m ng/m^3
Nonurban				
Continental				
General	10^3-10^4	20-80	1.1-2.2	-
California	10^3-10^4	39	2.8	0.48
Oregon	-	47	0.9	0.09
Colorado	10^2-10^4	14	1.1	0.11
Indiana	-	39	2.1	0.25
Maine	-	18	1.2	0.12
New York	-	29	1.8	0.25
So. Carolina	-	40	2.7	0.43
Maritime				
General	10^2-10^4	-	-	-
Pacific				
Offshore	10^2-10^4		1.5-6.1	-
Oahu, Hawaii	10^2-10^4		0.7-6.3	-
Urban				
Continental				
General	10^3-10^6	>100	7	-
Los Angeles	10^3-10^6	93	12.5	1.87
Portland	-	72	6.6	2.60
Denver	10^3-10^5	110	9.0	2.52
Minneapolis	10^3-10^5	70	6.1	1.18
Chatanooga	-	105	6.9	4.18
New York	-	105	8.9	3.63
Greenville, S.C.	-	76	7.4	7.49
Maritime				
Honolulu, Hawaii	10^2-10^4	40	2.3	0.59
San Juan, Puerto Rico	-	77	6.9	1.42

From Biological Effects of Atmospheric Pollution.
Particulate Polycyclic Organic Matter.
Committee on Biological Effects of Atmospheric Pollutants.
Division of Medical Sciences, National Academy of Sciences,
Washington, D.C. 1972.

One of the very difficult issues that confront the standard setting process is the appropriate use of analytic methods in determining workplace exposures. From the epidemiological studies cited, only one major study other than the coke oven studies quantified exposures to indicator polycyclic aromatic compounds to any meaningful degree. These difficulties have been well outlined in previous NIOSH criteria documents pertaining to coal tar products in 1977 and asphalt fumes in the same year.

The nature of the complex mixtures that are produced during the distillation of coal tar and petroleum products challenges the validity of an existing, accepted method of sampling for coal tar pitch volatiles via the cyclohexane soluble/or benzene soluble analytic technique. The shortcomings of this approach are that there may be either an over or under estimation of true carcinogenic potential given the nature of the specific polycyclic aromatic hydrocarbons present in the mixture. Anything soluble in cyclohexane in addition to PAHs will be measured. Analysis of asphalt fumes, as demonstrated by experiments by Niemeier (1985), suggest that a carcinogenic potential does exist for asphalt fumes; however, this does not correlate with the usual markers of the mixture of PAHs. Other compounds present in these fumes interacting with promoting hydrocarbons are as yet to be clearly identified.

An initial attempt to derive a Threshold Limit Value (TLV) for PAHs was carried out by the ACGIH in 1967 using an indirect estimate method. A standard of 0.2 mg/m^3 for CTPV was proposed.

It was measured as the benzene soluble fraction of the particulate collected assuming that PAHs would be desorbed along with other hydrocarbons by this method. This indirect method of measuring PAHs has remained the basis for threshold limit value (TLVs) in North America for controlling PAH exposures to coke oven emissions, asphalt fumes, and diesel fumes. The 1985-86 Ontario Ministry of Labor Time- Weighted Average Exposure Limit (TWAEL) for CTPV is 0.15 mg/m^3 for coke oven emissions (benzene soluble fraction of total particulate matter). It has been recognized that this indirect method lacks specificity and there has been some consideration of an exposure criteria for PAH's based on B(a)P measurement.

A TWAEL for B(a)P exposure of 0.15 ug/m^3 has been suggested in the U.S.S.R. This proposal is apparently based upon laboratory experiments with animals (Lindstedt and Sollenberg, 1982). In Sweden a TWAEL of 10 ug/m^3 for B(a)P was introduced in 1978, and reduced to 5 ug/m^3 in 1982. (Lindstedt and Sollenberg, 1982). An early Occupational Health and Safety Administration (OSHA) Advisory Committee in the U.S. had also recommended a B(a)P TWAEL Standard for coke oven emissions of 0.2 ug/m^3, but this was not adopted because of perceived technical problems with the B(a)P analysis (Gibson et al., 1983). Since then, NIOSH (1985) has proposed new methods for the sampling and analysis of PAH's (Methods 5506 and 5515) which are included in Appendix Ia and Ib. Since several groups in different countries (e.g., U.S.S.R., U.S.A., Sweden) have considered regulatory standards

for B(a)P, it is possible to use B(a)P exposure as a guide in the control of work place hazards from complex mixtures of PAHs even though true carcinogenic potential of certain complex mixtures may be underestimated.

A practical approach could be to use a dual sampling technique which incorporates both the traditional cyclohexane soluble method and newer techniques employing high performance liquid chromatography (HPLC) together with a UV detector and a fluorescence detector. This would involve the modification of the NIOSH method as outlined by Verma et al., (1982) in an analysis of polycyclic aromatic hydrocarbons in foundry environments. The advantage of a dual approach of incorporating a general method for measuring coal tar pitch volatiles and a more specific analysis for constituent PAHs gives an overall quantitative analytical method and a qualitative ability to guide the assessment for specific carcinogenic PAHs such as benzo[a]pyrene, anthracene and others. It would also be important not to recommend the use of benzene soluble methods despite its better extraction abilities since the cyclohexane soluble method presents much less of a health hazard to the analytic personnel. NIOSH methods 5506 and 5515 (1985) allow for the sampling and analysis of 17 specific PAHs from one environmental sample. These methods are included in Appendix I and should be adopted as standard methods in the final recommendation.

An accepted method for the measurement of dermal absorption has yet to be developed. This makes the process of establishing

a dermal exposure limit for coal tar products such as creosote unfeasible at the present time. Work practice standards must be used as a preventive intervention in such instances.

7.6 Risk Assessment and Recommendation for an Exposure Standard

In considering a specific time-weighted average exposure limit for coal tar products, petroleum pitch and asphalt, the lack of sound epidemiological data on which to base a low-dose risk estimate for human carcinogenesis makes this process extremely challenging. Statistical risk extrapolation techniques cannot be used without such data. We are left with a situation where the long-term human carcinogenic potential of complex mixtures containing PAH's is approximated but not well quantified at low doses by a comparative analysis with coke-oven emission data. The alternate approach of assessing the prevention of acute effects from these substances is a practical way to resolve some of the difficulties.

The health hazard evaluations carried out by NIOSH particularly by Hervin and Emmett (1976) and Gorman and Liss (1985), show that at the exposure levels of approximately 0.1 mg/m^3 cyclohexane soluble fraction or higher, acute effects such as keratoconjunctivitis and photosensitivity of the skin can be observed among groups of exposed workers. There have been no descriptive reports of health effects observed below this level.

Regarding asphalt fumes, only one report by Baylor and Weaver (1968) demonstrated any observed acute health effects; however, exposure was not quantified.

Given the weight of evidence concerning the carcinogenic potential of coal tar products and the preliminary animal data concerning the adverse reproductive effects of exposure to benzo[a]pyrene, it would be prudent to recommend a standard that minimizes exposure to these mixtures containing polycyclic aromatic compounds to the minimum detectable level in the absence of any information indicating a threshold level for safety. Ideally, no human should be exposed to carcinogenic materials or reproductive hazards at any level; however, given the current exposure levels to complex mixtures of PAH's in industry today, regulators may choose to adopt the ALARA principle or at least a minimum detectable level standard.

The ALARA approach to standard setting, although expedient in the past, has social policy implications which are important to consider in the contemporary context. The assumption of an "acceptable risk" for workers may not be acceptable now with the advent of modern industrial hygiene technology coupled with changing social and moral values. The exposure level that is "reasonably achievable" by industry must be defined in terms of primary prevention of adverse human health effects rather than comparative cost-benefit decision making approaches or other trade-off methods. Similarly, the limits of the sampling and analytic techniques which are feasible and "reasonably

achievable" in industry today should not be used as a factor to impede a rational standard setting process to maximally protect the health of workers. More specifically, the financial burden to industry to implement effective control programs and comply with strict exposure limits for the complex mixtures under consideration should not be used as an argument to justify an "acceptable risk" to health of exposed workers in Ontario.

The minimum detectable dose will vary according to the analytical techniques adopted, and with the advent of newer analytic procedures such as those that have been discussed in Section 7.5, standards can be adjusted appropriately. There is clearly sufficient scientific evidence to allow regulatory agencies to lower the standard from the current 0.2 mg/m^3 for coal tar pitch volatiles and 5 mg/m^3 for asphalt fumes to reduce the likelihood of acute health effects and carcinogenic risk described previously. The interpretation of the reproductive toxicity of B[a]P can be of a preliminary nature only, pending further human epidemiological studies, to confirm or refute the potential risk. Even though human scientific data are lacking at present, careful administrative controls should be put into place by regulations ensuring that exposure to complex mixtures of PAH's during pregnancy be kept to an absolute minimum, especially during the first trimester.

Air sampling should be a combination of the silver/glass fibre filter (Verma, 1982) or on the PTFE filter/washed XAD-2 method specified by NIOSH. Analytic methods should consist of

two parts:

1) Cyclohexane soluble fraction (mandatory)

2) Specific PAH quantification. (possibly optimal)

The latter procedure, done either by HPLC, Fluorescence/UV detection (NIOSH 5506) or capillary gas chromatography (NIOSH 5515), would give a measure of B[a]P concentration and 16 other PAH's. The fluorescence detector is both sensitive and selective to an amount as small as 50 pg of many PAH's injected on the column. The method is most amenable to the determination of trace amounts of PAH in mixtures of aliphatic compounds since the aliphatics are nonfluorescent. The capillary GC method is currently under further evaluation by NIOSH.

A practical safety margin of a factor of two to prevent acute health effects (.1 mg/m^3 x 0.5) would likely prevent any unpleasant acute effects from coal tar pitch volatiles. This is derived from the data of Hervin and Emmett (1976). Ideally, a safety factor of ten would be more desirable, however, current sampling procedures coupled with the cyclohexane soluble fraction method would allow for a minimum detectable level of approximately 0.01 mg/m^3. At workplace exposures at or below the minimum detectable level, acute health effects would likely not be a problem coupled with ambient environmental factors such as sunlight. Therefore, a proposed standard for a demonstrated human carcinogen could be set to this detection limit of 0.01 mg/m^3.

The risk reduction for human carcinogenesis that would be

achieved with a such an exposure standard cannot be accurately estimated due to the lack of a sound epidemiological dose-response model. Given the current assumptions about low-dose exposures to substances confirmed as carcinogens, zero health risk from occupational exposures cannot be assumed.

Considering the recent evidence of the carcinogenic potential of asphalt fumes and its lesser propensity to cause acute eye and skin irritation under usual working conditions, a ratio of 10 to 1 in the time-weighted average for occupational exposures would seem reasonable. This ratio is derived from the experimental animal carcinogenicity studies of Niemeier (1985) reviewed previously and does not consider the differential effects on the human eye and skin. In the absence of adequate data on humans, it is reasonable for practical purposes, to regard asphalt fumes as if they presented a carcinogenic risk to humans. The use of the expressions "for practical purposes" and "as if they presented a carcinogenic risk" indicates that, at the present time, a correlation between carcinogenicity in animals and possible human risk cannot be made on a purely scientific basis, but only pragmatically. Such a pragmatic correlation may be useful to regulatory agencies in making decisions related to the primary prevention of cancer.

In regard to the universality of the application of the animal data to the occupational environment, it is understood that the characteristics of crude oil from which roofing asphalts are derived, may vary from one drilling field to another.

Although not tested by Niemeier, it would be reasonable to assume that carcinogenic activity may also vary. For the purposes of standard setting, it would be prudent public health policy to assume that the carcinogenic activity of the various sources of asphalt fumes will not vary dramatically enough to prevent the general applicability of a single standard for exposure to asphalt fumes. If evidence becomes available to challenge this assumption in the future, regulatory agencies may wish to alter the exposure standard accordingly.

It is therefore proposed that an <u>interim</u> standard to limit occupational exposure to coal tar pitch volatiles from all forms of coal tar products including creosote should be 0.05 mg/m^3 cyclohexane soluble extract time-weighted average over an 8 hour working day. A STEL value is not proposed due to measurement limitations and insufficient toxicological data. This stringent criterion will necessitate a detailed analysis looking at indicator PAH compounds in the complex mixtures using the NIOSH methods described. With further data collection on PAH levels and profiles, consideration could be given to setting a standard using the newer methods.

With regard to asphalt fumes, it is recommended that a standard of 0.5 mg/m^3 time-weighted average over an 8 hour period, using the same sampling and analytic techniques, be adopted. The capillary GC method may provide more valid data as aliphatic hydrocarbons are the major components of asphalt fumes that exhibit co-carcinogen activity. Identification of other

carcinogenic compounds in these complex mixtures remains an area of urgent research.

Engineering controls such as local exhaust ventilation must be the prime means of control of workplace exposure to the above hazards. Careful consideration must be given to setting a workplace standard limiting dermal exposure to coal tar products such as creosote to zero exposure if product substitution is not feasible at this time. Components of such a standard would:

1. Require protective clothing and equipment (e.g., respirators, gloves).
2. Prohibit eating, drinking and smoking while applying wood preservatives.
3. Prohibit indoor application of wood preservatives.
4. Require proper care and disposal of work clothing and equipment.

Workers exposed in the health care and pharmaceutical industry should be included in the regulations. Farm workers exposed to these substances also should be included in the regulation. Administrative controls for reproductive risks should be implemented although scientific evidence regarding humans is lacking at this time.

It must be recognized that this recommendation for a standard for occupational exposures to coal tar products and bitumens is based on an incorporation of data on acute human effects and comparative risk estimates derived from animal data.

With the limitations of an epidemiologic data set on which to base risk projections, these proposals should be regarded as interim proposals. It is likely that within three to four years, an update of the Hammond (1976) study will be published taking into consideration some of the methodological concerns relating to adjustment for smoking habits and mixed exposures to coal tar and petroleum-based materials in the roofing industry. Well designed epidemiologic studies are urgently required to investigate other occupational groups exposed to substances reviewed in this document to define with greater confidence the risk for human cancer and adverse reproductive outcome. Review of the above proposed standards would be appropriate with the availability of this information.

GLOSSARY*

Adjuvant oil - A light mineral oil emulsified with certain vaccines to increase their effectiveness.

Agenesis - Absence of an organ due to non-appearance of its primordium in the embryo; imperfect development of a part.

Alicyclic - Referring to the aliphatic cyclic compounds (those with a ring structure) having the general formula C_nH_{2n}; cycloparaffinic, naphthenic.

Aliphatic - Referring to a hydrocarbon of open-chain structure, such as ethane, butane, octane, butene, and acetylene.

Alkanes - Saturated hydrocarbons with a general formula C_nH_{2n+2}, arranged in straight or branched open carbon chains; paraffins.

Alkenes - Hydrocarbons having one or more double bonds per molecule; olefins.

Alkylation - In petroleum refining, usually the union of an olefin (ethylene through pentene) with isobutane to yield high-octane, branched-chain paraffinic hydrocarbons. Alkylation may be accomplished as a thermal or as a catalytic reaction. Alkylation of benzene and other aromatics with olefins is also done to yield alkyl aromatics.

Anophthalmia - A developmental anomaly characterized by complete absence of the eyes (rare) or by the presence of vistigal eye.

Anthracene oil - A high boiling fraction from the distillation of coal tar.

Aromatic extract - (see solvent extract).

Aromatic petroleum naphthas - Mixtures of aromatic hydrocarbons derived from petroleum, principally alkyl derivation of benzene, indane, and naphthalene, generally not containing appreciable amounts of benzene..

Aromatic petroleum oils - Refined, semirefined, or unrefined petroleum products (solvent extracts or cracked materials) containing more than 40% aromatic compounds of widely varying complexity.

Aromatics - Hydrocarbon compounds containing one or more benzene rings.

Asphalt - A dark brown to black cement-like material in which the predominating constituents are bitumens which occur in nature or are obtained in petroleum processing.

Asphalt, air-blown - Asphalt produced by blowing air through residual asphalt or asphalt cement at temperatures ranging from 230 to 270°C (450-520°F). Such treatment improves the flow and weathering durability of the material. It is used for roofing, waterproofing and other industrial applications. Some paving

asphalts are also produced by light air-blowing.

Asphalt, petroleum (Straight run asphalt, Asphalt cement) - A very complex combination of high molecular weight organic compounds containing a relatively high proportion of hydrocarbons having carbon numbers predominantly greater than C_{25} with high carbon-to-hydrogen ratios. It also contains small amounts of various metals such as nickel, iron, or vanadium. It is obtained as the nonvolatile residue from distillation of crude oil or by separation as the raffinate from a residual oil in a deasphalting or decarbonization process.

Asphalt, roofing - An asphalt normally produced by air-blowing in several types and grades for use either as an interply adhesive in the construction of built-up roofs or as a coating asphalt or saturant in the preparation of asphalt shingles and roofing felts.

Asphalt, steam-refined - Asphalt produced by distillation in the presence of steam to reduce operating temperatures and prevent cracking.

Asphalt, thermal - Asphalt produced by a thermal cracking process.

Asphaltene - Any of the components of the bitumen in petroleums, petroleum products, asphalt cements, and solid native bitumens which are soluble in carbon disulfide but insoluble in paraffin naphthas.

BaP - Benzo(a)pyrene

Batch oil - A low-viscosity mineral oil used particularly in the manufacture of cordage.

Bitumen - The terms bitumen' and asphaltic bitumen' are used in Europe and are synonymous with the term asphalt' used in North America. The term bitumens refers to products derived from residues resulting from vacuum distillation of selected petroleum crude oils.

Bituminous materials - Naturally-occurring or manufactured dark brown or black solid, semisolid or viscous substances composed principally of hydrocarbons and their sulfur, oxygen and nitrogen derivatives, often associated with mineral matter.

Bunker C fuel oil - A heavy residual fuel oil used by ships, industry, and for large-scale heating installations; often referred to as No.6 fuel.

Cable oil - Mineral oil used as a dielectric for high voltage cables. High viscosity or heavy cable oil used to impregnate the paper wrapped around the conductor also contains rosin. Low viscosity or light cable oil used in the ducts of hollow core oil-filled cables usually contains aromatic extracts from solvent refining process.

Carbon black - Black, amorphous carbon, made by incomplete combustion or thermal decomposition of natural gas or of aromatic petroleum oils. Used in rubber compounding, inks, and paints. See also Furnace black.

Catalyst - A substance which affects, provokes, or accelerates reactions without itself being altered.

Catalytic cracking - A refining process which decomposes, rearranges, or combines hydrocarbon molecules by the aid of a catalyst.

Ceresin - A hard, brittle, microcrystalline wax, substantially free from oil, obtained by purifying ozokerite.

Charging stock - Oil that is to be treated in a particular unit.

Chemical treating - Refining effected by chemical reagents to remove or modify certain constituents, such as sulfides and acids, that have an unfavorable effect on finished oils.

Clarified oil - The heavy oil which has been taken from the bottom of a fractionator in a catalytic cracking process, and from which residual catalyst has been removed.

Coal tars - Byproducts of the destructive distillation of coal, called carbonization or coking.

Coal tar pitch - A dark brown black, shiny, amorphous residue produced in the distillation of coal tars.

Coke - A porous, cellular carbon residue produced from the destructive distillation of bituminous coal.

Coking - The high temperature carbonization of bituminous coal, coal tar pitch, petroleum residues, or other materials to produce coke.

Core oil - An oil suitable for use in making foundry cores.

Creosote - The distillate fractions or tar oils obtained by the fractional distillation of crude coal tars are commonly known as creosote.

Cracking - A refining process which decomposes, rearranges, or combines hydrocarbon molecules.

Crude oil - (See Crude petroleum.)

Crude petroleum - A naturally-occurring mixture consisting predominantly of hydrocarbons, but also containing sulfur, nitrogen or oxygen derivatives of hydrocarbons, which is removed from the earth in liquid state or is capable of being so removed.

Cutting oil (Cutting fluid, Cutting lubricant)- An oil used to lubricate and cool metal-cutting tools. Such oils may be water-soluble to water-insoluble. Usually, mineral oils are blended with lard oil or other oiliness or extreme-pressure agents to produce water-insoluble cutting oils, or with sulfinated products and other emulsifying agents to produce water-soluble cutting oils.

Cycloparaffins (Cycloalkanes) - Hydrocarbons of the general

formula C_nH_{2n}, containing nonaromatic closed chains of three or more carbon atoms; also known as naphthenes.

Deasphalting - (See Solvent deasphalting.).
Delayed coking - A thermal cracking process in which petroleum coke is produced by heating heavy petroleum fractions to 900°F at 35 psig.
Dewaxing - (See Solvent dewaxing.).
Diesel fuel - Fuel used for internal combustion in diesel engines; usually that fraction which distills after kerosine; similar to gas oil.
Distillate - That portion of a liquid which is removed as a vapor and condensed during a distillation process.
Distillation - Vaporization of a liquid and its subsequent condensation in a different chamber. The separation of one group of petroleum constituents from another by means of volatilization in some form of closed apparatus, such as a still, by the aid of heat.
Drawing lubricant - A mineral oil, residual oil, or other lubricant used in wire- and sheet metal-drawing operations.

Electrode - The device by which an electric current passes into or out of a cell, apparatus, or body.
Electrode binder - A bituminous material used to hold together the solid component, such as petroleum coke, of metallurgical electrodes.
Extender - A substance for increasing the volume of a rubber compound and decreasing the unit cost. Aromatic petroleum oils and waxes are often used for this purpose.
Extract - In solvent extraction processes, that portion of the oil which is dissolved in, and removed by, the selective solvent used. (See also Solvent extract.)

Feedstock - Crude oil or a fraction thereof to be charged to any process equipment.
Finishing processes - Secondary refining processes required to improve acceptability of primary refinery products. Processes may include solvent extraction, chemical oxidation, acid treatment, hydrogen treatment, clay refining, molecular sieves, and dehydration and filtration.
Fluid catalytic cracking (FCC) - A catalytic cracking process in which the oil is cracked in the presence of finely divided catalyst which is maintained in an aerated or fluidized state by the oil vapors.
Forging - A metal working process which increases the density, toughness and strength of metals by grain deformation. Forging may be performed either hot (150 to 315°C or 300 to 600°F) or cold.
Forging oils - Oils used as lubricants during forging.

Low viscosity mineral oils, black oils, and heavy residual oils are sometimes used in hot forging lubricants.

Foundry core - That part of a mold which forms the interior of a hollow casting.

Fractional distillation - The separation of the components of a liquid mixture by vaporizing and collecting the fractions, or cuts, which condense in different temperature ranges.

Fuel oil - Any liquid or liqueflable petroleum product burned for the generation of heat in a furnace or firebox, or for the generation of power in an engine, exclusive of oils with a flash point below 100°F (Tag closed-cup tester) and oils burned in cotton- or wool-wick burners. Domestic and industrial fuels generally include straight run and/or cracked distillate oils known as gas oil, diesel fuel, and light, medium, and heavy fuel oils. Residues of distillation and cracking are often present in the heavier commercial fuel oils such as Bunker C.

Furnace black - Carbon black made by incomplete combustion or thermal decomposition, in a furnace, of natural gas or other hydrocarbons, frequently highly aromatic residues from the cracking of petroleum.

Gas oil - A liquid petroleum distillate with a viscosity and boiling range between those of kerosine and lubricating oil.

Gastroschisis - Congential fissure of the abdominal wall.

Grinding oil - An oil used to lubricate, cool, and remove metal chips during metal grinding operations. (See also Cutting oil).

Heat transfer oil - A medium used for the transfer of heat at temperature levels above that of steam. Probably the most widely used medium is a high boiling petroleum fraction, usually in the gas oil range.

Heat treating oil - An oil used for cooling metal components in hardening and tempering operations.

Heterocyclic - A cyclic compound in which the ring is composed of atoms of at least two different elements.

Hydraulic fluid - A fluid of petroleum or nonpetroleum origin used in hydraulic systems, commonly based on mineral lubricating oils with low viscosity, low rate of change of viscosity with temperature, and low pour point.

Hydrocarbon - A compound containing only hydrogen and carbon. Such compounds form the principal constituents of petroleum.

Hydrocracking - A process combining cracking, or pyrolysis, with hydrogenation. Feedstocks can include crude oils, residua, petroleum tars, and asphalts.

Hydrodesulfurization - a desulfurization process in which the oil is treated with hydrogen.

Hydrodefining - A catalytic process of desulfurization and hydrogenation of a wide range of charge stocks, including the finishing of solvent extracted base lubricating oil stocks.

Hydrofinishing - A hydrogen treating process used for the finishing of solvent extracted lubricating oils.

Hydrogen processing (Hydrogen treating) - Treatment with hydrogen to modify the composition and properties of lubricating oils and other heavy stocks. According to severity, treatment may reduce concentrations of sulfur and nitrogen compounds, polycyclic aromatics, and other aromatic hydrocarbons.

Hydrorefining - Refining with the use of hydrogen, resulting in breakdown and saturation of aromatics, fall in viscosity, and almost complete elimination of sulfur.

Hydrotreating - A hydrodesulfurization process. Mild hydrotreating removes most nitrogen compounds; severe hydrotreating induces extensive hydrocracking in addition to saturation of aromatics and destructive hydrogenation of nonhydrocarbons.

Insulating oil - An oil used in circuit breakers, switches, transformers, and other electrical apparatus for insulating, cooling, or both. In general, such oils are well-refined petroleum distillates of low volatility, with high resistance to oxidation and sludging.

Isoparaffins - Paraffinic (saturated) hydrocarbons of branched-chain structure.

Jute batching oil - Oil used to soften and lubricate jute fiber before spinning.

Kerosine (Kerosene) - A petroleum distillate consisting of hydrocarbons having carbon numbers predominantly in the range of C_9 through C_{16} and boiling in the range of 150 to 290°C (302 to 554°F).

Kyphosis - Abnormally increased convexity in the curvative of the thoracic spine as viewed from the side.

Lubricant - A substance which may be interposed between the moving parts of machinery to reduce friction and prevent contact between the bearing surfaces.

Lubricating oil (Lube oil) - A fluid lubricant used to reduce friction between bearing surfaces, frequently produced from petroleum distillates or residues, often with additives to impart or improve certain required properties.

Metallurgical oil - A quenching or tempering oil used as a

coolant in the heat treatment of metals.

Metalworking oil - A lubricant used in forging, drawing, quenching, or cutting and grinding processes.

Medicinal oil - A highly refined white oil which meets standards for internal or pharmaceutical use.

Microcrystalline wax - Wax obtained from certain petroleum residues and having a finer and less apparent crystaline structure than paraffin wax.

Mineral oil - A general term referring to a wide range of products derived from mineral substances; highly refined white oil or medicinal oil from petroleum. In earlier British literature, Scottish shale oil.

Mineral oil, white - (See White oil.)

Mineral seal oil - A distillate cut between kerosine and gas oil. Used in signal lamps, as an absorption medium in gasoline recovery processes, and as a carrier for insecticides and sprays.

Mold oil - A lubricant used to insure easy parting of ceramic, glass, or other material from the mold in which it is cast.

Motor oil - An oil suitable for use in an engine crankcase; also an oil used to lubricate electric motors.

Mulespinner - A worker operating a spirning mule, a piece of equipment formerly used in the cotton and wool industries.

Naphthas - Numerous hydrocarbon mixtures in a broad boiling range, obtained by fractional distillation of either petroleum or coal tar. Not to be confused with naphthenes. (See Petroleum naphthas.)

Naphthenes - Cyclic or polycyclic hydrocarbons, also termed cycloparaffins or cycloalkanes, with a general formula of C_nH_{2n}. Not to be confused with naphthas.

Oil mist - A suspension of liquid droplets generated during use of machine tools or other high speed machinery by condensation of oil vaporized by heat at the contact point or by hot metal chips, centrifugal force fields associated with high speed rotation, or intentional spray lubrication.

Olefins - (See Alkenes.)

Ozokerite - A naturally occurring mineral wax or earth wax, usually dark brown in color and containing mineral matter and oil. On purification, it yields ceresin.

PAH - (See Polycyclic aromatic hydrocarbons.)

Paraffins - Saturated hydrocarbons of the general formula C_nH_{2n+2}, with straight or branched open chains. Also, inert waxy substances composed of saturated hydrocarbons obtained from petroleum.

Paraffin wax -Macrocrystalline wax usually produced from petroleum distillates by dewaxing processes, consisting

of a mixture of solid hydrocarbons in which the paraffin series predominates.

Petrochemical - A chemical product derived from petroleum or petroleum refinery streams. Examples include synthetic detergents, plastics and resins, agricultural chemicals, synthetic rubbers and fibers, and carbon black.

Petrolatum - A semisolid, unctuous petroleum wax containing substantial amounts of oil, produced during refining of residual stocks.

Petroleum - A naturally occurring material predominantly composed of mixtures of gaseous, liquid, and/or solid chemical compounds of carbon and hydrogen with or without other nonmetallic elements such as sulfur, oxygen, nitrogen.

Petroleum coke - A solid residue resulting from high temperature treatment of heavy petroleum fractions. It consists of carbonaceous material and contains some hydrocarbons having a high carbon-to-hydrogen ratio. Petroleum coke and its calcined product, artificial graphite, are suitable for production of metallurgical electrodes, motor brushes, dry cells, etc.

Petroleum naphthas - Refined, partly refined, or unrefined petroleum products, with specifications varying according to use, generally with not less than 95% distilling below 240°C (464°F). (See also Aromatic petroleum naphthas).

Petroleum pitch - Petroleum pitches are dark colored bituminous substances obtained as non-volatile residues from destructive distillation processes carried out during the refining of petroleum.

Petroleum wax - A product separated from petroleum which is solid or semisolid at 25°C (77°F) and consists essentially of a mixture of saturated hydrocarbons. (See Microcrystalline wax; Paraffin wax.)

Pitch - A viscous to solid thermoplastic residue remaining after the fractional distillation of tars or tar products from coal, wood, bone, etc. It is composed principally of aromatic hydrocarbons or their derivatives. This term should not be applied to petroleum products.

Polycyclic aromatic hydrocarbons (PAH) - Hydrocarbon compounds composed of a number of fused aromatic rings.

Printing oil - Mineral oil of suitable viscosity and boiling range used in letterpress newsprint inks as a vehicle for dispersed pigments such as carbon black.

Pterygium - A wing-like structure, applied especially an abnormal triangular fold of membrane in the interpalpebral fissure, extending from the conjunctiva to the cornea.

Pyrolysius - Decomposition of organic substances by heat.

Quenching oil - Mineral oil or other liquid used to remove heat rapidly from metals following heat treating processes.

Raffinate - In solvent extraction processes, that portion of the oil which remains undissolved and is not removed by the selective solvent.

Refinery - A plant, with all its included equipment, for manufacturing finished or semifinished products from crude oil.

Refining - The separation of crude oil into its component parts, and the manufacture therefrom of products needed for the market. Important processes in refining are distillation, cracking, chemical treating, and solvent extraction.

Reforming - The thermal or catalytic conversion of naphtha into more volatile products of higher octane number. It represents the total effect of numerous reactions, such as cracking, polymerization, dehydrogenation, and isomerization, taking place simultaneously.

Residue (Residuum) - The heavy fraction or bottoms remaining undistilled after volatilization of all lower boiling constituents.

Rubber extender oils (Extending oils, Extenders) - Highly aromatic petroleum oils, usually aromatic extracts containing 80 to 90% aromatics, added to the latex in large quantities (up to 50 parts per hundred in rubber) to extend the bulk of the rubber.

Rubber processing oils - Mineral oils such as light naphthenic feedstocks containing about 40% aromatics, added in relatively small quantities during the milling of polymerized rubber to improve properties.

Saturated hydrocarbons - A hydrocarbon of such molecular structure that all adjacent carbon atoms are connected by not more than one valence or bond.

Slack wax - The soft, oily crude wax obtained from the pressing of paraffin distillate or wax distillate.

Solvent - A substance, usually a liquid, used for dissolving another substance.

Solvent deasphalting - A process for removing asphaltic and resinous materials from reduced crude oils, lubricating oil stocks, gas oils, or middle distillates through the extraction or precipitant action of solvents in which asphalt is insoluble. The principal deasphalting solvents are low-molecular-weight hydrocarbons, particularly liquid propane, and oxygenated compounds, such as alcohols and esters.

Solvent dewaxing - A process for removing wax from oils by means of solvents in which the wax is insoluble.

Solvent extract - A complex combination of hydrocarbons obtained as the extract from a solvent refining

process. Distillate solvent extracts consist predominantly of aromatic hydrocarbons and are likely to contain 5 wt % or more of 4- to 6-membered condensed ring aromatic hydrocarbons.

Solvent extraction - The process of separating materials of different chemical type, by means of selective solvent action, into a fraction soluble in the solvent (extract), and an insoluble residue (raffinate). Solvents used to treat lubricating stock include furfural, phenol, and liquid sulfur dioxide.

Solvent refining - (See Solvent extraction.)

Spindle oil - A well-refined oil suitable for the lubrication of light, high-speed machinery such as encountered in the textile industry.

Spray oil - A petroleum product of low viscosity, usually similar to lubricating oil, used to combat pests which attack trees, etc.

Straight run product - A product produced by the primary distillation of crude oil.

Sweetening - A process by which petroleum products are improved in odor and color by oxidizing or removing the sulfur-containing and unsaturated compounds.

Tar - A thick brown to black liquid mixture of hydrocarbons and their derivatives obtained by distillation of coal, petroleum, wood, or other vegetable or mineral materials; the bottoms product from any cracking operation.

Tempering oil - (See Heat treating oil.)

Textile oil - Oil used to lubricate textile machinery; also, a wide assortment of nonlubricating oils used in the textile industry to render fabrics and yarns pliable to facilitate weaving and spinning operations.

Thermal cracking - A refining process which decomposes, rearranges, or combines hydrocarbon molecules by the application of heat, without the aid of catalysts.

Thermal reforming - A process using heat, but no catalyst, to effect molecular rearrangement of low-octane naphtha into gasoline of higher antiknock quality.

Topping - The distillation of crude oil to remove light fractions only.

Transformer oil - An electrical insulating oil used in transformers to dispatch heat and to act as an insulant.

Transmission lubricant - An oil or other fluid used to lubricate the transmission of an automobile.

Unsaturated hydrocarbon (unsaturate) - A hydrocarbon of such molecular structure that at least two adjacent carbon atoms are connected by two or three valences or bonds.

Vacuum distillation - Distillation under reduced pressure, thereby reducing the boiling temperature sufficiently to prevent decomposition or cracking of the material being distilled.

Vehicle - A liquid with which solids are mixed for use.

Wax, paraffin - (See Paraffin wax.)

Wax pressing - The process of separating wax and oil from paraffin wax distillates by use of a filter press.

White oil - A group of highly refined, colorless hydrocarbon oils of low volatility, and covering a wide range of viscosities, widely used for the lubrication of food and textile machinery.

* From Bingham et al. (1980), McNeil D (1983).

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FORMULA: Table 1

M.W.: Table 1

POLYNUCLEAR AROMATIC HYDROCARBONS

METHOD: 5506
ISSUED: 5/15/85

OSHA: proposed for B[a]P: 0.2 µg/m³
ACGIH: suspect carcinogen (B[a]P)

PROPERTIES: Table 1

COMPOUNDS:
- acenaphthene
- acenaphthylene
- anthracene
- benz[a]anthracene
- benzo[b]fluoranthene
- benzo[k]fluoranthene
- benzo[ghi]perylene
- benzo[a]pyrene
- benzo[e]pyrene
- chrysene
- dibenz[a,h]anthracene
- fluoranthene
- fluorene
- indeno[1,2,3-cd]pyrene
- naphthalene
- phenanthrene
- pyrene

SYNONYMS: PAH; PNA; also see Table 2.

SAMPLING

SAMPLER: FILTER + SORBENT
(2-µm, 37-mm PTFE + washed XAD-2, 100 mg/50 mg)

FLOW RATE: 2 L/min

VOL-MIN: 200 L
-MAX: 1000 L

SHIPMENT: transfer filters to culture tubes; wrap sorbent and culture tubes in Al foil; ship @ 0 °C

SAMPLE STABILITY: unknown; protect from heat and UV radiation

FIELD BLANKS: 10% (≥3) of samples
MEDIA BLANKS: 6 to 10

AREA SAMPLES: 8 replicates on preweighed filters for solvent selection

ACCURACY

RANGE STUDIED, BIAS, AND OVERALL PRECISION (s_r): not measured

MEASUREMENT

METHOD: HPLC, FLUORESCENCE/UV DETECTION

ANALYTE: compounds above

EXTRACTION: 5 mL organic solvent appropriate to sample matrix (step 7)

COLUMN: 15 cm x 4.6 mm, reverse phase, 5-µm C_{18}

INJECTION VOLUME: 10 to 50 µL

MOBILE PHASE: H_2O/CH_3CN gradient @ ambient temperature

FLOW RATE: 1.0 mL/min

DETECTORS: UV @ 254 nm; fluorescence @ 340 nm (excitation), 425 nm (emission)

CALIBRATION: external standards in CH_3CN

RANGE, LOD AND PRECISION (s_r): EVALUATION OF METHOD

APPLICABILITY: The working range for B[a]P is 1 to 50 µg/m³ for a 400-L air sample. Specific sample sets may require modification in filter extraction solvent, choice of measurement method, and measurement conditions (see EVALUATION OF METHOD).

INTERFERENCES: Any compound which elutes at the same HPLC retention time may interfere. Heat, ozone, NO_2, or UV light may cause sample degradation.

OTHER METHODS: This revises P&CAM 206 and 251 [1]. The spectrophotometric methods, P&CAM 184 and 186 [1], have not been revised. Also see Method 5515 (GC).

REAGENTS:

1. Filter extraction solvent: benzene,* cyclohexane, methylene chloride, or other appropriate solvents, pesticide grade grade (step 7).
2. Water, distilled, deionized, degassed.
3. Acetonitrile, HPLC grade, degassed.
4. PAH reference standards,* appropriate to the PAH-containing matrix sampled.
5. Calibration stock solution, 0.25 mg/mL.* Check purity of each PAH reference standard by GC/FID, HPLC/fluorescence and/or melting point. Purify, if necessary, by recrystallization. Weigh 25 mg of each PAH into a 100-mL volumetric flask; dilute to volume with acetonitrile. Stable six months if refrigerated and protected from light.

*See SPECIAL PRECAUTIONS.

EQUIPMENT:

1. Sampler:
   a. Filter. PTFE-laminated membrane filter, 2-µm pore size, 37-mm diameter (ZEFLOUR, Membrana, Pleasanton, CA or equivalent), backed by a gasket (37-mm OD, 32-mm ID) cut from a cellulose support pad, in cassette filter holder.
      NOTE 1: If sampling is to be done in bright sunlight, use opaque or foil-wrapped cassettes to prevent sample degradation.
      NOTE 2: Take filters to be preweighed from the filter package and allow to equilibrate 24 hrs with laboratory atmosphere before taring.
   b. Sorbent tube, connected to filter with minimum length PVC tubing. Plastic caps are required after sampling. Washed XAD-2 resin (front = 100 mg; back = 50 mg) (Supelco ORBO 43 or equivalent). Pressure drop at 2 L/min airflow 1.6 to 2 kPa (15 to 20 cm H_2O).
2. Personal sampling pump capable of operating for 8 hrs at 2 L/min, with flexible connecting tubing.
3. Aluminum foil.
4. Vial, scintillation, 20-mL, glass, PTFE-lined cap.
5. Refrigerant, bagged.
6. Culture tubes, PTFE-lined screw cap, 13-mm x 100-mm.
7. Forceps.
8. Filters, 0.45-µm, PTFE or nylon (for filtering sample solutions).
9. Pipet, 5-mL.
10. Syringe or micropipets, 1- to 100-µL.
11. Ultrasonic bath.
12. HPLC, with gradient capability, fluorescence (excitation @ 240 nm, emission @ 425 nm) and UV (254 nm) detectors in series, electronic integrator, and column [HC-ODS-SILX (Perkin-Elmer Corp.), Vydac 201TP (The Separations Group) or equivalent; see page 5506-1].
13. Volumetric flasks, 10- and 100-mL.
14. Lighting in laboratory: incandescent or UV-shielded fluorescent.
15. Kuderna-Danish extractor.

SPECIAL PRECAUTIONS: Treat benzene and all polynuclear aromatic hydrocarbons as carcinogens. Neat compounds should be weighed in a glove box. Spent samples and unused standards are toxic waste. Regularly check counter tops and equipment with "black light" for fluorescence as an indicator of contamination by PAH.

SAMPLING:

1. Calibrate each personal sampling pump with a representative sampler in line.
2. Take personal samples at 2 L/min for a total sample size of 200 to 1000 L. Take a concurrent set of eight replicate area samples at 2 to 4 L/min on preweighed, 2-µm PTFE filters in an area of highest expected PAH concentration.
   NOTE: The area samples are needed for solvent selection (step 7).
3. Immediately after sampling, transfer the filter carefully with forceps to a scintillation vial. Hold filter at edge to avoid disturbing the deposit. Cap the scintillation vial and wrap it in aluminum foil.
   NOTE: This step is necessary to avoid loss of analytes due to sublimation and degradation by light.
4. Cap the sorbent tube and wrap it in aluminum foil.
5. Ship to laboratory in insulated container with bagged refrigerant.

SAMPLE PREPARATION:

NOTE: UV light may degrade PAH. Use yellow, UV-absorbing shields for fluorescent lights or use incandescent lighting.

6. Refrigerate samples upon receipt at laboratory.
7. Determine optimum extraction solvent.
   a. Allow the preweighed area filter samples to equilibrate 24 hrs with the laboratory atmosphere.
   b. Weigh the area filters. Determine total weight collected on each.
   c. Extract the first pair of area filters with acetonitrile, the second with benzene, the third with cyclohexane, and the fourth with methylene chloride, according to step 8.
      NOTE: Use alternate solvents, if appropriate. PAH of interest may be entrained within, and adsorbed by, particulate matter collected on the filter. It is necessary to determine the solvent which maximizes recovery of the PAH from each sample matrix. For example, methylene chloride [2,3] and benzene:ethanol (4:1 v/v) [4] have been recommended for extraction of PAH from diesel exhaust particulate.
   d. Analyze the extracts for the PAH of interest (steps 10 through 18). Normalize the total mass of PAH found to the mass of sample collected.
   e. Choose the solvent which gives the highest recovery of PAH of interest. Use the solvent chosen to extract the personal filter samples.
8. Extract filters.
   a. Add 5.0 mL of the solvent chosen in step 7 to each scintillation vial containing a filter. Start media and reagent blanks at this step.
   b. Cap and let sit 15 to 20 min in an ultrasonic bath.
      NOTE 1: Soxhlet extraction may be required when large amounts of highly adsorptive particulate matter (e.g., fly ash or diesel soot) are present.
      NOTE 2: The sample must be dissolved in acetonitrile for chromatography. If needed, perform solvent exchange as follows:
      CAUTION: To avoid loss of volatile components, do not allow the sample to go to dryness at any time.
      (1) After filtration (step 10), take the sample to near dryness in a Kuderna-Danish extractor.
      (2) Add ca. 1 mL acetonitrile, take to near dryness, and adjust final volume to 1.0 mL with acetonitrile and filter again.
9. Desorb PAH from sorbent.
   a. Score each sorbent tube with a file in front of the front (larger) sorbent section. Break tube at score line.

b. Transfer glass wool plug and front sorbent section to a culture tube. Discard the foam plug. Transfer back sorbent section to a second culture tube.
c. Add 5.0 mL acetonitrile to each culture tube. Cap the culture tubes.
d. Allow samples to sit for 30 min. Swirl occasionally.

10. Filter all sample extracts through an 0.45-μm membrane filter.

CALIBRATION AND QUALITY CONTROL:

11. Calibrate daily with at least five working standards.
    a. Dilute aliquots of calibration stock solution with acetonitrile in 10-mL volumetric flasks (e.g., to 2.5, 0.5, 0.1, 0.02, and 0.002 μg/mL).
    b. Intersperse working standards and samples in the measurements.
    c. Prepare calibration graphs (peak area vs. μg of each PAH per sample).
12. Recovery and desorption efficiency.
    a. Determine recovery (R) from filters and desorption efficiency (DE) from sorbent tubes at least once for each lot of filters and sorbent tubes used in the range of interest.
       (1) Filters. Using a microliter syringe or micropipette, spike four filters at each of five concentration levels with a mixture of the analytes. Allow the filters to dry in the dark overnight. Analyze the filters (steps 8, 10, and 14 through 16. Prepare graphs of R vs. amounts found.
           NOTE: This step may not be used for some highly adsorptive particulate matrices for which calibration by the method of standard additions may be more accurate.
       (2) Sorbent tubes. Transfer an unused front sorbent section to a culture tube. Prepare a total of 24 culture tubes in order to measure DE at five concentration levels plus blanks in quadruplicate. Using a microliter syringe or micropipette, add calibration stock solution directly to sorbent. Cap culture tubes and allow to stand overnight. Analyze (steps 9, 10, and 14 through 16). Prepare graphs of DE vs. amounts found.
    b. Check R and DE at two levels for each sample set, in duplicate. Repeat determination of R and DE graphs if checks do not agree to within ±5% of DE graph.
13. Analyze at least three field blanks for each sample medium.

MEASUREMENT:

14. Set HPLC according to manufacturer's recommendations and to conditions on page 5506-1. Equilibrate column at 60% CH_3CN/40% H_2O at 1.0 mL/min for 15 min before injecting first sample.
15. Inject sample aliquot. Start mobile phase gradient:
    a. Linear gradient 60% CH_3CN to 100% CH_3CN, 20 min.
    b. Hold at 100% CH_3CN for 20 min.
       NOTE: Hold longer if necessary to prevent carryover of background, e.g., from coal dust.
    c. Linear gradient to initial condition, 5 min.
16. Measure peak areas.
    NOTE 1: Approximate retention times appear in Table 3.
    NOTE 2: If peak area is above the calibration range, dilute with appropriate solvent, reanalyze, and apply dilution factor in calculations.
    NOTE 3: If sample has many interferences, additional sample cleanup may be necessary. Many cleanup procedures have been published. Liquid-liquid partitioning between cyclohexane and nitromethane [5,6] is widely used, but other techniques may be more appropriate for specific samples.

CALCULATIONS:

17. Read the mass, µg (corrected for R or DE) of each analyte found on the filter (W) and front sorbent (W_f) and back sorbent (W_b) sections, and on the average media blank filter (B) and front sorbent (B_f) and back sorbent (B_b) sections from the calibration graphs.
18. Calculate concentration, C (µg/m³), in air as the sum of the particulate concentration and the vapor concentration using the actual air volume sampled, V (L).

$$C = \frac{(W - B + W_f + W_b - B_f - B_b) \cdot 10^3}{V}, \ \mu g/m^3.$$

NOTE: W_f and W_b include analyte originally collected on the filter as particulate, then volatilized during sampling. This can be a significant fraction for many PAH (e.g:, fluoranthane, naphthalene, fluorene, anthracene, phenanthrene).

EVALUATION OF METHOD:

The fluorescence detector used in this method is both sensitive and selective. The detector can "see" as little as 50 pg of many PAH injected on the column. LODs for the 17 analytes range from 50 to 350 ng per sample. It does not respond to non-fluorescent molecules such as aliphatics. The method is, therefore, most amenable to determination of trace amounts of PAH in mixtures of aliphatic compounds. Successful applications include: aluminum reduction facilities, asphalt fume, coal gasification plants, coal liquefaction plants, coal tar pitch, coke oven emissions, creosote treatment facilities, diesel exhaust, graphite electrode manufacturing, petroleum pitch, and roofing tearoff operations.

This method has been evaluated by analyzing spiked filters, spiked sorbent tubes, and complete spiked sampling trains through which were drawn 500 L of air [7]. Each of the three groups was spiked with each analyte at two concentration levels in sextuplicate. Particular note should be made that the effect of particulate matter has not been evaluated, and every sampling matrix is unique. The data on the following page were obtained on spiked samplers stored refrigerated in the dark for three months followed by measurement with HPLC.

COMPOUND	CALIBRATION RANGE (µg per sample)	LOD (µg per sample)	MEASUREMENT PRECISION SPIKED[a]	SPIKED + AIR[b]
1. ACENAPHTHENE	2.0 - 13	0.8	.058 S	.093 (50)
2. ACENAPHTHYLENE	1.0 - 100	0.35	.032 S	.075 (100)
3. ANTHRACENE	0.4 - 13	0.05	.039 S	.037 (5)
4. BENZ[a]ANTHRACENE	0.4 - 13	0.15	.032 F	.084 (5)
5. BENZO[b]FLUORANTHENE	0.4 - 12	0.1	.027 F	.028 (10)
6. BENZO[k]FLUORANTHENE	0.4 - 13	0.15	.025 F	.027 (1)
7. BENZO[ghi]PERYLENE	0.5 - 25	0.2	.031 F	.029 (10)
8. BENZO[a]PYRENE	0.4 - 14	0.2	.027 F	.029 (5)
9. BENZO[e]PYRENE	0.5 - 13	0.2	(c)	(c)
10. CHRYSENE	0.4 - 12	0.15	.039 F	.024 (5)
11. DIBENZ[a,h]ANTHRACENE	0.5 - 25	0.2	.026 F	.029 (10)
12. FLUORANTHENE	0.4 - 13	0.15	.026 S	.050 (10)
13. FLUORENE	0.7 - 13	0.25	.031 S	.090 (10)
14. INDENO[1,2,3-cd]PYRENE	0.5 - 12	0.2	.044 F	.032 (10)
15. NAPHTHALENE	0.6 - 13	0.25	.041 S	.125 (50)
16. PHENANTHRENE	0.4 - 13	0.1	.036 S	.070 (2)
17. PYRENE	0.5 - 13	0.2	(c)	(c)

[a]RSD for filter (F) where volatilization is nil or for sorbent (S) where substantial volatilization may occur during sampling.

[b]RSD determined at the µg level shown in parenthesis for a spiked filter followed by a sorbent tube. After spiking, laboratory air was drawn through the sampling train at 2 L/min for 4 hrs.

[c]Not determined.

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METHOD REVISED BY: B. R. Belinky and E. J. Slick, NIOSH/DPSE.

5/15/85

Table 1. Formulae and physical properties.

COMPOUND (by M.W.)	EMPIRICAL FORMULA	MOLECULAR WEIGHT	DETECTOR	MELTING POINT (°C)	BOILING POINT (°C)*	REF.
1. NAPHTHALENE	$C_{10}H_8$	128.17	UV	80	218	[9]
2. ACENAPHTHYLENE	$C_{12}H_8$	152.20	UV	92-93	265-275	[10]
3. ACENAPHTHENE	$C_{12}H_{10}$	154.21	UV	96.2	279	[10]
4. FLUORENE	$C_{13}H_{10}$	166.22	UV	116	293-295	[9]
5. ANTHRACENE	$C_{14}H_{10}$	178.23	UV	218	340	[9]
6. PHENANTHRENE	$C_{14}H_{10}$	178.23	UV	100	340	[9]
7. FLUORANTHENE	$C_{16}H_{10}$	202.26	FL	110	—	[9]
8. PYRENE	$C_{16}H_{10}$	202.26	FL	156	399	[9]
9. BENZ[a]ANTHRACENE	$C_{18}H_{12}$	228.29	FL	158-159	—	[9]
10. CHRYSENE	$C_{18}H_{12}$	228.29	UV	255-256	—	[9]
11. BENZO[b]FLUORANTHENE	$C_{20}H_{12}$	252.32	FL	168	—	[9]
12. BENZO[k]FLUORANTHENE	$C_{20}H_{12}$	252.32	FL	217	480	[10]
13. BENZO[a]PYRENE	$C_{20}H_{12}$	252.32	FL	177	—	[9]
14. BENZO[e]PYRENE	$C_{20}H_{12}$	252.32	FL	178-179	—	[9]
15. BENZO[ghi]PERYLENE	$C_{22}H_{12}$	276.34	FL	273	—	[9]
16. INDENO[1,2,3-cd]PYRENE	$C_{22}H_{12}$	276.34	FL	161.5-163	—	[8]
17. DIBENZ[a,h]ANTHRACENE	$C_{22}H_{14}$	278.35	FL	262	—	[9]

*Many of these compounds will sublime.

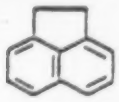
Table 2. Synonyms.

COMPOUND (alphabetically)	SYNONYMS
1. ACENAPHTHENE	CAS# 83-32-9
2. ACENAPHTHYLENE	CAS# 208-96-8
3. ANTHRACENE	CAS# 120-12-7
4. BENZ[a]ANTHRACENE	1,2-benzanthracene; benzo[b]phenanthrene; 2,3-benzophenanthrene; tetraphene; CAS# 56-55-3
5. BENZO[b]FLUORANTHENE	3,4-benzofluoranthene; 2,3-benzofluoranthene; benz[e]acephenanthrylene; B[b]F; CAS# 205-99-2
6. BENZO[k]FLUORANTHENE	11,12-benzofluoranthene; CAS# 207-08-9
7. BENZO[ghi]PERYLENE	1,12-benzoperylene; CAS# 191-24-2
8. BENZO[a]PYRENE	3,4-benzopyrene; 6,7-benzopyrene; B[a]P; BP; CAS# 50-32-8
9. BENZO[e]PYRENE	1,2-benzopyrene; 4,5-benzopyrene; B[e]P; CAS# 192-97-2
10. CHRYSENE	1,2-benzophenanthrene; benzo[a]phenanthrene; CAS# 218-01-9
11. DIBENZ[a,h]ANTHRACENE	1,2,5,6-dibenzanthracene; CAS# 53-70-3
12. FLUORANTHENE	benzo[jk]fluorene; CAS# 206-44-0
13. FLUORENE	CAS# 86-73-7
14. INDENO[1,2,3-cd]PYRENE	2,3-phenylenepyrene; CAS# 193-39-5
15. NAPHTHALENE	naphthene; CAS# 91-20-3
16. PHENANTHRENE	CAS# 85-01-8
17. PYRENE	benzo[def]phenanthrene; CAS#129-00-0

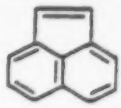
Table 3. Approximate PAH retention times.

COMPOUND	RETENTION TIME (min)*
1. NAPHTHALENE	2.4
2. ACENAPHTHALENE	2.8
3. ACENAPHTHENE	3.6
4. FLUORENE	3.9
5. PHENANTHRENE	4.7
6. ANTHRACENE	5.8
7. FLUORANTHENE	6.8
8. PYRENE	7.7
9. BENZ[a]ANTHRACENE	11.2
10. CHRYSENE	12.1
11. BENZO[e]PYRENE	14.0
12. BENZO[b]FLUORANTHENE	14.8
13. BENZO[k]FLUORANTHENE	16.5
14. BENZO[a]PYRENE	17.3
15. DIBENZ[a,h]ANTHRACENE	20.0
16. BENZO[ghi]PERYLENE	20.0
17. INDENO[1,2,3-cd]PYRENE	21.2

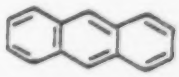
*NOTE: Determined with a Perkin-Elmer HC-OOS-SILX column. Actual retention times will vary with individual columns and column age.



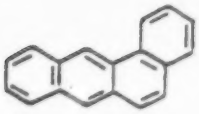
ACENAPHTHENE



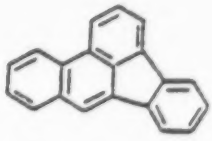
ACENAPHTHYLENE



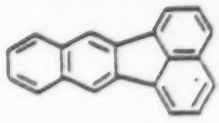
ANTHRACENE



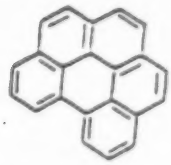
BENZ(a)ANTHRACENE



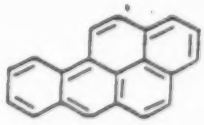
BENZO(b)FLUORANTHENE



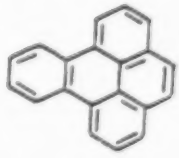
BENZO(k)FLUORANTHENE



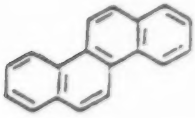
BENZO(g h i)PERYLENE



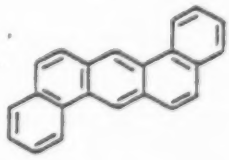
BENZO(a)PYRENE



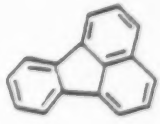
BENZO(e)PYRENE



CHRYSENE

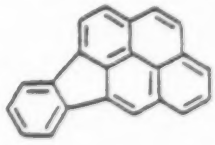


DIBENZ(a,h)ANTHRACENE



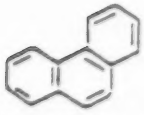
FLUORANTHENE

FLUORENE

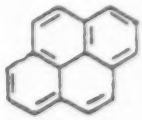


INDENO(1,2,3-c d)PYRENE

NAPHTHALENE



PHENANTHRENE



PYRENE

Figure 1. Structures of PAH.

FORMULA: Table 1

M.W.: Table 1

POLYNUCLEAR AROMATIC HYDROCARBONS

METHOD: 5515
ISSUED: 5/15/85

OSHA: proposed for B[a]P: 0.2 ug/m³
ACGIH: suspect carcinogen (B[a]P)

PROPERTIES: Table 1

COMPOUNDS:
- acenaphthene
- acenaphthylene
- anthracene
- benz[a]anthracene
- benzo[b]fluoranthene
- benzo[k]fluoranthene
- benzo[ghi]perylene
- benzo[a]pyrene
- benzo[e]pyrene
- chrysene
- dibenz[a,h]anthracene
- fluoranthene
- fluorene
- indeno[1,2,3-cd]pyrene
- naphthalene
- phenanthrene
- pyrene

SYNONYMS: PAH; PNA; also see Table 2.

SAMPLING

SAMPLER: FILTER + SORBENT
(2-um, 37-mm PTFE + washed XAD-2, 100 mg/50 mg)

FLOW RATE: 2 L/min

VOL-MIN: 200 L
-MAX: 1000 L

SHIPMENT: transfer filters to culture tubes; wrap sorbent and culture tubes in Al foil; ship @ 0 °C

SAMPLE STABILITY: unknown; protect from heat and UV radiation

FIELD BLANKS: 10% (≥3) of samples
MEDIA BLANKS: 6 to 10

AREA SAMPLES: 8 replicates on preweighed filters for solvent selection

ACCURACY

RANGE STUDIED, BIAS, and OVERALL PRECISION (s_r): not measured

MEASUREMENT

!METHOD: GAS CHROMATOGRAPHY, CAPILLARY COLUMN, FID

!ANALYTE: compounds above

!EXTRACTION: 5 mL organic solvent appropriate to sample matrix (step 7)

!INJECTION VOLUME: 4 µL; 10:1 split

!COLUMN: 30 m x 0.32 mm ID, fused silica capillary, 1 um DB-5

!TEMPERATURE-INJECTOR: 200 °C
-DETECTOR: 250 °C
-PROGRAM: 130 to 290 °C @ 4 °C/min

!GASES-CARRIER: He @ 1 mL/min
-MAKEUP: He @ 20 mL/min

!LOD: ca. 0.3 to 0.5 ug per sample [1]

!CALIBRATION: external standards in toluene

!RANGE, LOD, and PRECISION (s_r): EVALUATION OF METHOD

APPLICABILITY: The working range for B[a]P is 3 to 150 µg/m³ for a 400-L air sample by HPLC. Specific sample sets may require modification in filter extraction solvent, choice of measurement method, and measurement conditions.

INTERFERENCES: Any compound which elutes at the same GC retention time may interfere. Heat, ozone, NO_2, or UV light may cause sample degradation.

OTHER METHODS: This revises P&CAM 23 [2]. The spectrophotometric methods, P&CAM 184 and 196 [2], have not been revised. See also Method 5506 (HPLC).

REAGENTS:

1. Filter extraction solvent: acetonitrile, benzene,* cyclohexane, methylene chloride, or other appropriate solvents, pesticide grade (step 7).
2. Toluene, pesticide grade.
3. Water, distilled, deionized.
4. PAH reference standards,* appropriate to the PAH-containing matrix sampled.
5. Calibration stock solution, 0.25 mg/mL.* Check purity of each PAH reference standard by GC/FID, HPLC/fluorescence and/or melting point. Purify, if necessary, by recrystallization. Weigh 25 mg of each PAH into a 100-mL volumetric flask; dilute to volume with toluene. Stable six months if refrigerated and protected from light.
6. Helium, prepurified.
7. Hydrogen, dry.
8. Air, filtered.

*See SPECIAL PRECAUTIONS.

EQUIPMENT:

1. Sampler:
   a. Filter. PTFE-laminated membrane filter, 2-µm pore size, 37-mm diameter (ZEFLOUR, Membrana, Pleasanton, CA or equivalent), backed by a gasket (37-mm OD, 32-mm ID) cut from a cellulose support pad, in cassette filter holder.
      NOTE 1: If sampling is to be done in bright sunlight, use opaque or foil-wrapped cassettes to prevent sample degradation.
      NOTE 2: Take filters to be preweighed from the filter package and allow to equilibrate 24 hrs with laboratory atmosphere before taring.
   b. Sorbent tube, connected to filter with minimum length PVC tubing. Plastic caps are required after sampling. Washed XAD-2 resin (front = 100 mg; back = 50 mg) (Supelco ORBO 43 or equivalent). Pressure drop at 2 L/min airflow 1.6 to 2 kPa (15 to 20 cm H_2O).
2. Personal sampling pump capable of operating for 8 hrs at 2 L/min, with flexible connecting tubing.
3. Aluminum foil.
4. Vial, scintillation, 20-mL, glass, PTFE-lined cap.
5. Refrigerant, bagged.
6. Culture tubes, PTFE-lined screw cap, 13-mm x 100-mm.
7. Forceps.
8. Filters, 0.45-µm, PTFE or nylon (for filtering sample solutions).
9. Pipet, 5-mL.
10. Syringe or micropipets, 1- to 100-µL.
11. Ultrasonic bath.
12. Gas chromatograph with FID, electronic integrator, and capillary column (page 5515-1).
13. Volumetric flasks, 10- and 100-mL.
14. Lighting in laboratory: incandescent or UV-shielded fluorescent.

SPECIAL PRECAUTIONS: Treat benzene and all polynuclear aromatic hydrocarbons as carcinogens. Neat compounds should be weighed in a glove box. Spent samples and unused standards are toxic waste. Regularly check counter tops and equipment with "black light" for fluorescence as an indicator of contamination by PAH.

SAMPLING:

1. Calibrate each personal sampling pump with a representative sampler in line.
2. Take personal samples at 2 L/min for a total sample size of 200 to 1000 L. Take a concurrent set of eight replicate area samples at 2 to 4 L/min on preweighed, 2-µm PTFE filters in an area of highest expected PAH concentration.
   NOTE: The area samples are needed for solvent selection (step 7).

3. Immediately after sampling, transfer the filter carefully with forceps to a scintillation vial. Hold filter at edge to avoid disturbing the deposit. Cap the scintillation vial and wrap it in aluminum foil.
   NOTE: This step is necessary to avoid loss of analytes due to sublimation and degradation by light.
4. Cap the sorbent tube and wrap it in aluminum foil.
5. Ship to laboratory in insulated container with bagged refrigerant.

SAMPLE PREPARATION:

NOTE: UV light may degrade PAH. Use yellow, UV-absorbing shields for fluorescent lights or use incandescent lighting.

6. Refrigerate samples upon receipt at laboratory.
7. Determine optimum extraction solvent.
   a. Allow the preweighed area filter samples to equilibrate 24 hrs with the laboratory atmosphere.
   b. Weigh the area filters. Determine total weight collected on each.
   c. Extract the first pair of area filters with acetonitrile, the second with benzene, the third with cyclohexane, and the fourth with methylene chloride, according to step 8.
      NOTE: Use alternate solvents, if appropriate. PAH of interest may be entrained within, and adsorbed by, particulate matter collected on the filter. It is necessary to determine the solvent which maximizes recovery of the PAH from each sample matrix. For example, methylene chloride [3,4] and benzene:ethanol (4:1 v/v) [5] have been recommended for extraction of PAH from diesel exhaust particulate.
   d. Analyze the extracts for the PAH of interest (steps 10 through 18). Normalize the total mass of PAH found to the mass of sample collected.
   e. Choose the solvent which gives the highest recovery of PAH of interest. Use the solvent chosen to extract the personal filter samples.
8. Extract filters.
   a. Add 5.0 mL of the solvent chosen in step 7 to each scintillation vial containing a filter. Start media and reagent blanks at this step.
   b. Cap and let sit 15 to 20 min in an ultrasonic bath.
      NOTE: Soxhlet extraction may be required when large amounts of highly adsorptive particulate matter (e.g., fly ash or diesel soot) are present.
9. Desorb PAH from sorbent.
   a. Score each sorbent tube with a file in front of the front (larger) sorbent section. Break tube at score line.
   b. Transfer glass wool plug and front sorbent section to a culture tube. Discard the foam plug. Transfer back sorbent section to a second culture tube.
   c. Add 5.0 mL toluene to each culture tube. Cap the culture tubes.
   d. Allow samples to sit for 30 min. Swirl occasionally.
10. Filter all sample extracts through an 0.45-µm membrane filter.

CALIBRATION AND QUALITY CONTROL:

11. Calibrate daily with at least five working standards.
   a. Dilute aliquots of calibration stock solution with toluene in 10-mL volumetric flasks (e.g., to 5, 1, 0.2, 0.05, and 0.005 µg/mL).
   b. Intersperse working standards and samples in the measurements.
   c. Prepare calibration graphs (peak area vs. µg of each PAH per sample).

12. Recovery and desorption efficiency.
    a. Determine recovery (R) from filters and desorption efficiency (DE) from sorbent tubes at least once for each lot of filters and sorbent tubes used in the range of interest.
        (1) Filters. Using a microliter syringe or micropipette, spike four filters at each of five concentration levels with calibration stock solution. Allow the filters to dry in the dark overnight. Analyze the filters (steps 8, 10, and 14 through 16). Prepare graphs of R vs. amounts found.
            NOTE: This step may not be used for some highly adsorptive particulate matrices for which calibration by the method of standard additions may be more accurate.
        (2) Sorbent tubes. Transfer an unused front sorbent section to a culture tube. Prepare a total of 24 culture tubes in order to measure DE at five concentration levels plus blanks in quadruplicate. Using a microliter syringe or micropipette, add calibration stock solution directly to sorbent. Cap culture tubes and allow to stand overnight. Analyze (steps 9, 10, and 14 through 16). Prepare graphs of DE vs. amounts found.
    b. Check R and DE at two levels for each sample set, in duplicate. Repeat determination of R and DE graphs if checks do not agree to within ±5% of DE graph.
13. Analyze at least three field blanks for each sample medium.

MEASUREMENT:

14. Set GC according to manufacturer's recommendations and to the conditions on page 5515-1:
15. Inject sample aliquot. Start temperature program.
16. Measure peak areas.
    NOTE 1: Approximate retention times appear in Table 3.
    NOTE 2: If peak area is above the calibration range, dilute with appropriate solvent, reanalyze, and apply dilution factor in calculations.
    NOTE 3: If sample has many interferences, additional sample cleanup may be necessary. Many cleanup procedures have been published. Liquid-liquid partitioning between cyclohexane and nitromethane [6,7] is widely used, but other techniques may be more appropriate for specific samples.

CALCULATIONS:

17. Read the mass, ug (corrected for R or DE) of each analyte found on the filter (W) and front sorbent (W_f) and back sorbent (W_b) sections, and on the average media blank filter (B) and front sorbent (B_f) and back sorbent (B_b) sections from the calibration graphs.
18. Calculate concentration, C ($\mu g/m^3$), in air as the sum of the particulate concentration and the vapor concentration using the actual air volume sampled, V (L).

$$C = \frac{(W - B + W_f + W_b - B_f - B_b) \cdot 10^3}{V}, \ \mu g/m^3.$$

NOTE: W_f and W_b include analyte originally collected on the filter as particulate, then volatilized during sampling. This can be a significant fraction for many PAH (e.g., fluoranthane, naphthalene, fluorene, anthracene, phenanthrene).

EVALUATION OF METHOD:

Due to large interferences which arose while utilizing NIOSH Method P&CAM 206 for samples collected during asphalt roofing oprations, the gas chromatographic capillary column method was developed. The GC method has been evaluated using several hundred field filter and sorbent tube sampling trains. To date, no statistical studies have been initiated. Overall, standard spiked filters and sorbent tubes have produced reproducible measurement calibration graphs.

5/15/85

Table 1. Formulae and physical properties.

COMPOUND (by M.W.)	EMPIRICAL FORMULA	MOLECULAR WEIGHT	DETECTOR	MELTING POINT (°C)	BOILING POINT (°C)*	REF.
1. NAPHTHALENE	$C_{10}H_8$	128.17	UV	80	218	[10]
2. ACENAPHTHYLENE	$C_{12}H_8$	152.20	UV	92-93	265-275	[11]
3. ACENAPHTHENE	$C_{12}H_{10}$	154.21	UV	96.2	279	[11]
4. FLUORENE	$C_{13}H_{10}$	166.22	UV	116	293-295	[10]
5. ANTHRACENE	$C_{14}H_{10}$	178.23	UV	218	340	[10]
6. PHENANTHRENE	$C_{14}H_{10}$	178.23	UV	100	340	[10]
7. FLUORANTHENE	$C_{16}H_{10}$	202.26	FL	110	--	[10]
8. PYRENE	$C_{16}H_{10}$	202.26	FL	156	399	[10]
9. BENZ[a]ANTHRACENE	$C_{18}H_{12}$	228.29	FL	158-159	--	[10]
10. CHRYSENE	$C_{18}H_{12}$	228.29	UV	255-256	--	[10]
11. BENZO[b]FLUORANTHENE	$C_{20}H_{12}$	252.32	FL	168	--	[10]
12. BENZO[k]FLUORANTHENE	$C_{20}H_{12}$	252.32	FL	217	480	[11]
13. BENZO[a]PYRENE	$C_{20}H_{12}$	252.32	FL	177	--	[10]
14. BENZO[e]PYRENE	$C_{20}H_{12}$	252.32	FL	178-179	--	[10]
15. BENZO[ghi]PERYLENE	$C_{22}H_{12}$	276.34	FL	273	--	[10]
16. INDENO[1,2,3-cd]PYRENE	$C_{22}H_{12}$	276.34	FL	161.5-163	--	[9]
17. DIBENZ[a,h]ANTHRACENE	$C_{22}H_{14}$	278.35	FL	262	--	[10]

*Many of these compounds will sublime.

Table 2. Synonyms.

COMPOUND (alphabetically)	SYNONYMS
1. ACENAPHTHENE	CAS# 83-32-9
2. ACENAPHTHYLENE	CAS# 208-96-8
3. ANTHRACENE	CAS# 120-12-7
4. BENZ[a]ANTHRACENE	1,2-benzanthracene; benzo[b]phenanthrene; 2,3-benzophenanthrene; tetraphene; CAS# 56-55-3
5. BENZO[b]FLUORANTHENE	3,4-benzofluoranthene; 2,3-benzofluoranthene; benz[e]acephenanthrylene; B[b]F; CAS# 205-99-2
6. BENZO[k]FLUORANTHENE	11,12-benzofluoranthene; CAS# 207-08-9
7. BENZO[ghi]PERYLENE	1,12-benzoperylene; CAS# 191-24-2
8. BENZO[a]PYRENE	3,4-benzopyrene; 6,7-benzopyrene; B[a]P; BP; CAS# 50-32-8
9. BENZO[e]PYRENE	1,2-benzopyrene; 4,5-benzopyrene; B[e]P; CAS# 192-97-2
10. CHRYSENE	1,2-benzophenanthrene; benzo[a]phenanthrene; CAS# 218-01-9
11. DIBENZ[a,h]ANTHRACENE	1,2,5,6-dibenzanthracene; CAS# 53-70-3
12. FLUORANTHENE	benzo[jk]fluorene; CAS# 206-44-0
13. FLUORENE	CAS# 86-73-7
14. INDENO[1,2,3-cd]PYRENE	2,3-phenylenepyrene; CAS# 193-39-5
15. NAPHTHALENE	naphthene; CAS# 91-20-3
16. PHENANTHRENE	CAS# 85-01-8
17. PYRENE	benzo[def]phenanthrene; CAS#129-00-0

The method has been applied to the following sample matrices with semi-quantitative results using three separate particulate extraction solvents (benzene, cyclohexane, acetonitrile): aluminum reduction facilities, asphalt fume, coal gasification plants, coal liquefaction plants, coal tar pitch, coke oven emissions, creosote treatment facilities, diesel exhaust, graphite electrode manufacturing, petroleum pitch, and roofing tearoff operations.

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[8] Backup Data Report for Method 5506, Analytical Report for NIOSH Sequence 4170 (NIOSH, DPSE, MRSB, unpublished, March 16, 1984).
[9] Studt., P., Liebigs Ann. Chem., 528 (1978).
[10] Clar, E. Polycyclic Hydrocarbons, Academic Press (1964).
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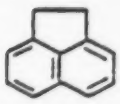
METHOD REVISED BY: B. R. Belinky and E. J. Slick, NIOSH/DPSE; J. C. Holt, D. E. Bilak, and J. B. Perkins, UBTL, Inc.

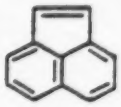
Table 3. Approximate PAH retention times.

COMPOUND	RETENTION TIME (min)*
1. NAPHTHALENE	not available
2. ACENAPHTHALENE	7.66
3. ACENAPHTHENE	8.37
4. FLUORENE	10.5
5. PHENANTHRENE	15.0
6. ANTHRACENE	15.3
7. FLUORANTHENE	21.4
8. PYRENE	22.6
9. BENZ[a]ANTHRACENE	29.4
10. CHRYSENE	29.6
11. BENZO[e]PYRENE	36.4
12. BENZO[b]FLUORANTHENE	35.1
13. BENZO[k]FLUORANTHENE	35.2
14. BENZO[a]PYRENE	36.6
15. DIBENZ[a,h]ANTHRACENE	43.9
16. BENZO[ghi]PERYLENE	45.6
17. INDENO[1,2,3-cd]PYRENE	43.6

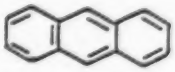
*NOTE: Actual retention times will vary with individual columns and column age.



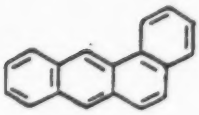
ACENAPHTHENE



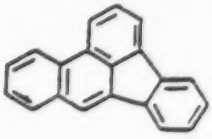
ACENAPHTHYLENE



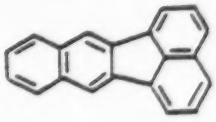
ANTHRACENE



BENZ(a)ANTHRACENE

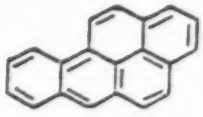


BENZO(b)FLUORANTHENE

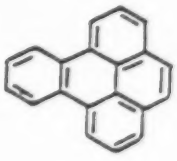


BENZO(k)FLUORANTHENE

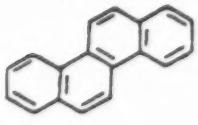
BENZO(g h i)PERYLENE



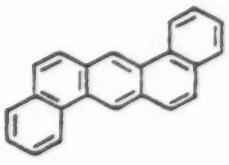
BENZO(a)PYRENE



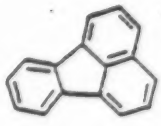
BENZO(e)PYRENE



CHRYSENE

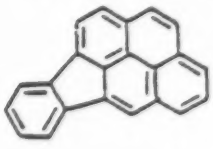


DIBENZ(a,h)ANTHRACENE

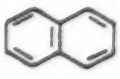


FLUORANTHENE

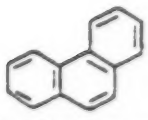
FLUORENE



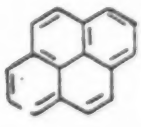
INDENO(1,2,3-c d)PYRENE



NAPHTHALENE



PHENANTHRENE



PYRENE

Figure 1. Structures for PAH.

APPENDIX II

IARC CRITERIA FOR EVALUATING THE CARCINOGENIC RISK OF CHEMICALS OR COMPLEX MIXTURES

(a) Evaluation of carcinogenicity studies in experimental animals

The evidence of carcinogenicity in experimental animals is assessed and judged to fall into one of four groups, defined as follows:

(1) Sufficient evidence of carcinogenicity is provided when there is an increased incidence of malignant tumours: (a) in multiple species or strains; or (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumour, or age at onset. Additional evidence may be provided by data on dose-response effects.

(2) Limited evidence of carcinogenicity is available when the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain or experiment; or (b) the experiments

are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) the neoplasms produced often occur spontaneously and, in the past, have been difficult to classify as malignant by histological criteria alone (e.g., lung adenomas and adenocarcinomas and liver tumours in certain strains of mice).

(3) Inadequate evidence is available when, because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect.

(4) No evidence applies when several adequate studies are available which show that, within the limits of the tests used, the chemical or complex mixture is not carcinogenic.

(b) Evidence for activity in short term-tests

An overall assessment of the evidence for genetic activity is judged to fall into one of four categories, defined as follows:

(i) Sufficient evidence is provided by at least

three positive entries, one of which must involve mammalian cells *in vitro* or *in vivo* and which must include at least two of three end-points - DNA damage, mutation and chromosomal effects.

(ii) Limited evidence is provided by at least two positive entries.

(iii) Inadequate evidence is available when there is only one positive entry or when there are too few data to permit an evaluation of an absence of genetic activity or when there are unexplained, inconsistent findings in different test systems.

(iv) No evidence applies when there are only negative entries; these must include entries for at least two end-points and two levels of biological complexity, one of which must involve mammalian cells *in vitro* or *in vivo*.

(c) Evidence for carcinogenicity from studies in humans

The evidence for carcinogenicity from studies in humans is assessed and judged to fall into one of four groups, defined as follows:

1. Sufficient evidence of carcinogenicity indicates that there is a causal relationship between the exposure and human cancer.

2. Limited evidence of carcinogenicity indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded.

3. Inadequate evidence, which applies to both positive and negative evidence, indicates that one of two conditions prevailed: (a) there are few pertinent data; or (b) the available studies, while showing evidence of association, do not exclude chance, bias or confounding.

4. No evidence applies when several adequate studies are available which do not show evidence of carcinogenicity.

For many of the chemicals (or complex mixtures) evaluated for which there is sufficient evidence of carcinogenicity in animals, data relating to carcinognicity for humans are either insufficient or nonexistent. In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans. The use of the expressions for practical purposes' and as if they presented a carcinogenic risk' indicates that, at the present time, a correlation between carcinogenicity in animals and possible human risk cannot be made on a purely

scientific basis, but only pragmatically. Such a pragmatic correlation may be useful to regulatory agencies in making decisions related to the primary prevention of cancer.